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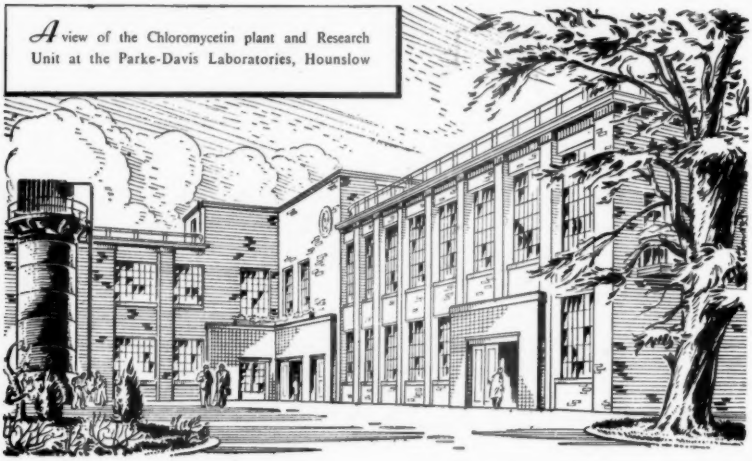

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Section of Anæsthetics

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[*March* 2, 1951]

DISCUSSION ON THE USE OF HYPOTENSIVE DRUGS IN SURGERY

Dr. G. E. Hale Enderby (*Royal National Orthopædic Hospital, Queen Victoria Hospital, East Grinstead and Metropolitan Ear, Nose and Throat Hospital*): I propose to limit my remarks to the use of hypotensive drugs in operative surgery to produce a relatively bloodless field. I shall refer almost entirely to hexamethonium bromide because I find this drug superior to any other I have used, but pentamethonium iodide has been used on several occasions, and all the preliminary work was done with it. The effect on bleeding is achieved by paralysis of the autonomic ganglia causing a fall in blood pressure. To this is added the effects of posture, causing a further reduction of pressure, and an ischæmia of the raised end of the body, with a congestion of the more dependent parts. The ischæmic area is relatively bloodless.

This work is experimental, and the drug should be used with caution until its full possibilities have been explored. Its use does not necessarily mean a reduction in bleeding and it is quite unpardonable to employ it unless the full implications of autonomic paralysis are understood, and the anæsthetist feels competent to deal with this condition, and to make use of it. The anæsthetist who does employ this technique must give it his undivided attention. He must make repeated blood-pressure estimations and watch carefully the pulse, the colour and the site of operation. Only by so doing can he maintain the necessary degree of safety. Such patients cannot be left unattended even for short periods.

Dr. John Gillies states that a systolic blood pressure of about 60 mm.Hg will maintain a capillary circulation sufficient for cellular respiration and metabolism in all the vital organs provided the blood is well oxygenated, and provided vasodilatation is assured. It is therefore the vasodilator state which is important for the safety of the patient. This is a great departure from normal physiology, but it should not be judged on physiological grounds only for in anæsthesia there is always a divergence from normal which must never be so great at any point as to render the return difficult or impossible. I have accepted the physiological disturbance I am producing as inevitable in order to obtain an effect which, at times, is essential. This may make all the difference to the success of the operation, and may enable the anæsthetist to take a greater share in this success or failure, and therefore a greater pride in his work. I feel, too, that provided the ill-effects from this technique are not greater than the ill-effects which we observe from what is known as a normal anæsthetic, then we are justified in proceeding. At the same time it is well to bear in mind that what we have come to consider a normal anæsthetic does not mean a normal blood pressure. A study will show that the usual anæsthetic and surgical procedures practised on patients are themselves liable to cause wide fluctuations in blood pressure, the effect most commonly observed being pressor.

Technique.—The effects of posture: When vasomotor control has been abolished by hexamethonium bromide the adoption of a posture which allows blood to gravitate into the legs will reduce blood pressure. The reverse Trendelenburg and the lateral and prone jack-knife positions are examples of this. This is the basis of the operating theatre technique. The outline of the anæsthetic and the management of such a case is as follows:

Premedication is by omnopon and scopolamine, or morphia and atropine if over 60 years of age. Induction is by intravenous thiopentone and for intubation is assisted by a muscle-relaxant drug. These drugs do occasionally assist the autonomic ganglionic blocking action of the methonium compounds. Maintenance of anæsthesia is by nitrous oxide and oxygen (2 : 1) in a semi-closed circle absorber, assisted occasionally by very small doses of ether, but intermittent thiopentone is the basal anæsthetic delivered through a Gordh needle which is always used. Most commonly this is placed on the dorsum of the foot, but other useful regions are the antecubital veins and those on the dorsum of the hand. Cyclopropane is avoided. Trichlorethylene appears to be good, but usually there is no need for agents stronger than nitrous oxide in the conduct of these cases.

When anæsthesia has been stabilized and the patient is on the operating table the correct posture is adopted and the drug given. The initial dose of hexamethonium bromide varies with age and pre-operative blood pressure, the normal young adult receiving 50 mg. and the effects assessed in three minutes. Patients over 40 receive 30–40 mg. and hypertensives, arteriosclerotics and those over 60 begin with 20 mg.

There are two distinct manœuvres which must be employed to obtain a dry surgical field. One is to lower the blood pressure to the optimum of 55–65 mm.Hg, the other to elevate the site of operation. This causes the dependent parts to become congested with prominent veins whilst the elevated part is pale and ischæmic. Sir Henry Dale has very aptly described this as "postural ischæmia", and I would emphasize that it is a most important factor in reducing bleeding. For operations on the head and neck and upper part of the trunk, the patient is tipped into the reverse Trendelenburg position after having made sure of an adequate foot rest to the operation table. This position fulfils both requirements. The degree of reverse Trendelenburg tilt varies with the response of patients to the drug. The young healthy patient who has received an initial dose of 50 mg. usually shows an increase of pulse-rate to 120–140 per minute and postural hypotension is not profound. Further doses of hexamethonium bromide up to a total of 150–200 mg. are occasionally necessary, and the maintenance of extreme posture is essential to preserve hypotension of a surgically useful degree. In Fig. 1 there was a steep reverse Trendelenburg position and the initial dose of pentamethonium iodide had to be supplemented on three further occasions up to a total of 80 mg. The pulse-rate rose from 70 to about 120. The postural ischæmia was excellent, and of great assistance surgically.

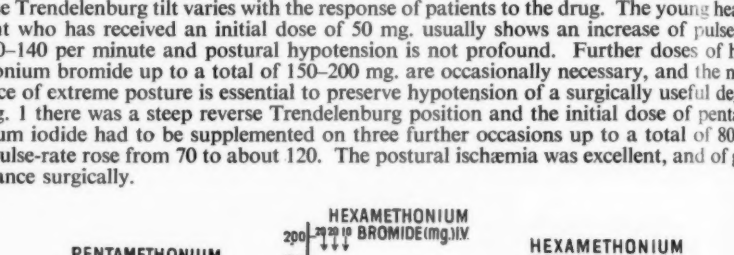

FIG. 1. FIG. 2. FIG. 3.

FIG. 1.—Blood pressure ($\vee$ = systolic, $\wedge$ = diastolic) and pulse (•----•) during removal of frontal sinus, ethmoidectomy and skin graft in a woman aged 30, supine, with 35 degrees to 40 degrees reverse Trendelenburg tilt of operating-table. Operation field very satisfactory with cavities dry for grafting.

FIG. 2.—Controlled hypotension with well-marked postural ischæmia in a hypertensive arteriosclerotic male aged 71, during operation for forehead flap to facial defect. Patient supine, with 5 degrees to 7 degrees reverse Trendelenburg tilt of operating-table. Initial dose of hexamethonium bromide 20 mg. Total dose 50 mg.

FIG. 3.—Inadequate control of hypotension in a strong healthy male aged 39, during fenestration operation. Patient supine with 40 degrees reverse Trendelenburg tilt of operating-table. Total dose of hexamethonium bromide 160 mg. Bleeding was moderate in amount, but not satisfactory for drilling the fenestra.

The older patient, particularly if hypertensive and arteriosclerotic, shows little rise of pulse-rate, indeed occasionally a bradycardia, and the postural hypotension is profound. This type of patient may require an increase of an initially small dose of hexamethonium bromide but a moderate degree of posture suffices to maintain an adequate hypotension which when once stabilized at the optimum shows little tendency to alter for half to one hour. This type is much easier to manage when once stabilized, but the initial response to the drug can be dramatic, and needs most careful watching. In Fig. 2 a moderate posture was sufficient to produce an optimal hypotension. The pulse-rate remained steady at 80–90 per minute which was little different from the normal pre-operative level. The postural ischæmia was excellent, and the forehead flap was never congested, or showed other signs of circulatory embarrassment.

In Fig. 3 it proved impossible to maintain an adequate hypotension and the surgical field received only moderate assistance.

With a patient in the steep reverse Trendelenburg position the possibility of cerebral ischæmia is vitally important. In all my cases, and more particularly when in this position, I have carefully controlled the hypotension to 55–65 mm.Hg and have not observed any effects either during the operation or afterwards which might lead me to believe the brain was damaged, or had been working under a dangerous handicap.

The abdomen and pelvis are more difficult regions to render ischæmic. In the upper abdomen a slight reverse Trendelenburg tilt assisted by a little elevation of the gall-bladder bridge is sufficient to produce an optimal hypotension after the incision has been made. The incision releases the negative pressure normally transmitted to the abdominal cavity by the respiratory action of the thorax and diaphragm, and so reduces the venous return to the heart and the blood pressure. For upper abdominal intraperitoneal operations the existence of a low pressure assists the surgeon, although they are not usually bloody operations. The raising of the gall-bladder bridge in these cases is a most potent factor in producing hypotension. This has been observed by other workers using different techniques, e.g. epidural and spinal blocks.

When the site of operation is on the lower trunk or in the pelvis, there is a conflict in principle between the need to tip one way to reduce the blood pressure and the other to drain the area. Thus in the pelvis it is best to have half of each, and to maintain a horizontal position, assisted by lowered legs only. In this way it is often possible to maintain an adequate hypotension, but it is impossible to obtain much postural ischæmia.

Perineal operations where the legs are raised in the lithotomy position present another problem. I would like the gynæcologists to work with the patient in the prone jack-knife position. Elevated legs raise the blood pressure, and at the same time the blood drains from them into the operation area. Consequently it may be impossible to obtain an optimal hypotension, and there is never any postural ischæmia. However, bleeding is often reduced enough to be of assistance surgically, but the effect seldom compares with that observed in other regions where drainage can be employed. Furthermore, at the end of operation when the legs are lowered the blood pressure may fall alarmingly, and may require assistance from a vasoconstrictor such as methedrine to restore it to a safe level.

With the patient prone it is possible to employ the jack-knife position on a suitable operation table. This position causes a profound fall of blood pressure, often without extreme posture. One effect is noticed consistently, that operations on the spinal canal encounter marked venous bleeding, especially in the lumbar and sacral regions. The venous nature is quite obvious, and has on many occasions caused me to check the oxygenation of the patient. It is considered that in this position there is back pressure via the abdominal veins on to the dural veins which, therefore, are more prominent and bleed easily. This controlled hypotension is primarily a redistribution of blood so that venous channels are fuller than normal unless they are drained, and here is the reason for elevating the site of operation because by so doing the venous blood drains to the more dependent parts. If in these cases the patient can be placed in a position which relieves the pressure on the abdomen, and at the same time allows drainage to occur, hæmorrhage should be reduced.

I have now dealt at some length with the postures employed to reduce blood pressure and obtain an ischæmic field. All these entail lowering the legs and pooling the blood. Pooling is perhaps too forceful a description because there is no reservoir action which the name implies, but rather a reduction of venous return to the heart, which factor is responsible for all the effects observed in all the various positions. It appears probable that the greater the capacity on the venous side of the peripheral circulation, the lower will the blood pressure fall. This may account for the greater fall observed in older patients. Here it is necessary to bring to your attention one further factor of great importance, and not widely realized. Positive pressure respiration, either controlled or assisted, will, in the absence of vasomotor control, produce a great fall in blood pressure. This factor was responsible for many strange things observed from time to time before it was understood, but, now its importance has been realized, it has on occasions been used with advantage to maintain an adequate hypotension. Here again its mode of action is probably the same as posture, namely by raising the intrapulmonary pressure, the venous return to the heart is diminished, and at the same time the suction and force pump action of the thoracic wall and diaphragm are no longer operative, and there is a reduction in the venous return.

The state of the cardiac muscle during hypotension is vitally important. Electrocardiographic studies in normal and hypotensive states have been performed by Dr. Douglas Robertson. In the small series which he has so far investigated there has been no evidence of coronary ischæmia in either young or old patients when the pressure has been between 60–70 mm.Hg.

Dangers of this technique.—The response may be, and in the older patient often is, dramatic, and the blood pressure, even with a minor degree of posture, falls very low. It is seldom necessary to reduce B.P. below the level of 55–65 mm.Hg. When the B.P. falls below this it

can be restored by reversal of posture, and if necessary by a vasoconstrictor such as methedrine. If I have to use methedrine I use only 4–8 mg. intravenously, which is usually enough to return the pressure to the desired level. Doses larger than this cause a greater rise of pressure with the danger of reactionary hæmorrhage.

Another great danger arises from hæmorrhage. Let me stress that this will, in the absence of vasomotor control, lead to an incredibly severe hypotension. When produced in this way hypotension is dangerous, for there is no longer an adequate volume of blood in the circulation. It is most essential to replace blood loss by an equivalent volume, and this will immediately restore the original pressure. This effect of intravenous replacement is dramatic, and is one which I sometimes employ as an indication of the vascular requirement in those cases where I know, because of posture or other factors, I shall encounter bleeding during the course of an operation. Let me stress also that when the drug has once been given to a patient for better or worse it will be there for the next three to four hours, during which time it will be effective. The blood pressure can be restored by methedrine or other vasoconstrictor, but this does not replace the vasomotor control which the body has lost. Under these circumstances the anæsthetist must act as interpreter of the body's needs, just as he does for more obvious requirements during unconsciousness. I would stress again that a vasoconstrictor is no substitute for vasomotor control.

The last danger is an inadequate airway. This is fundamental in anæsthesia, but it is even more essential when pressure is low, for in this condition oxygen deficiency will strike with deadly accuracy.

This technique has been used in 250 cases (Enderby, G. E. H., and Pelmore, J. F., 1951, *Lancet* (i), 663). When it is possible to combine a hypotension of 55–65 mm.Hg with an elevated site of operation, bleeding is minimal. Using hexamethonium bromide 85% of patients can be controlled at 55–80 mm.Hg and even at the relatively high pressure of 80, bleeding is often considerably reduced, and hæmostasis more quickly and satisfactorily obtained. Reactionary hæmorrhage does not appear to be increased, but it is essential to ensure a slow return of blood pressure to guard against this.

In conclusion I would again draw the attention of those who intend to use this hypotensive technique to the dangers of vasomotor paralysis. These are:

(1) Uncontrolled hypotension with a pressure below 55 mm.Hg.
(2) Hæmorrhage which will quickly lead to a severe and dangerous hypotension.
(3) Inadequate airway.

Dr. M. H. Armstrong Davison (*Department of Anæsthetics, Royal Victoria Infirmary, Newcastle upon Tyne*):

The idea of lowering the blood pressure in order to produce a bloodless field for operation is not a new one; indeed, it was early found that, when chloroform was used, hæmorrhage was less than when ether was the anæsthetic administered. However, there are a number of dangers associated with lowering the blood pressure and, although most surgeons would probably prefer a bloodless field for every operation, in the vast majority of cases the patient's best interests can be served by maintaining the blood pressure as near normal as possible, and by correcting blood loss by transfusion. In certain cases, however, the technique of controlled hypotension may be justifiable: when, for instance, an operation is required to correct some disorder which is making the patient's life miserable, and when the success of that operation is put in hazard because the surgeon cannot obtain a sufficiently clear field in which to exercise his skill. In such a case, it may be, not only that controlled hypotension may become a recognized practice, but also that the use of pentamethonium, or some similar drug, may commend itself to anæsthetists more than spinal analgesia, or heavy basal narcosis, partly because it seems to be more easily controlled, and partly because it may not entail some of the risks, both operative and post-operative, which are associated with the other methods.

Pentamethonium iodide.—Pentamethonium iodide (bis-trimethylammonium pentane di-iodide) entered the anæsthetist's ken clinging to the skirts of its bigger sister, decamethonium iodide. This entry was heralded by Organe, Paton and Zaimis (1949) in a paper in which the muscular relaxant action of decamethonium was described. It was there stated that pentamethonium or "C5" was the antidote to decamethonium or "C10". It was also stated that, in doses of 20 to 40 mg. intravenously, pentamethonium did not alter the blood pressure of conscious persons in the supine position, but did render such persons posture sensitive, falls of 20 to 35 mm.Hg occurring when they stood up. It was therefore thought that this drug might be used to reduce blood pressure and hæmorrhage, especially in hypertensive patients, in whom the effect was expected to be more dramatic, but also in others, taking advantage of postural sensitivity. The first case was undertaken in July 1949; the first intimation in the Press being an article (Davison, 1950) in which it was sought to warn

anæsthetists against the use of pentamethonium as an antidote to decamethonium, since it was found, contrary to the findings of Arnold and Rosenheim (1949*b*), that, in the anæsthetized patient, a profound fall in blood pressure was likely to occur, not only in hypertensives, but in others, and in spite of postural safeguards (Figs. 1, 2, 3, 4).

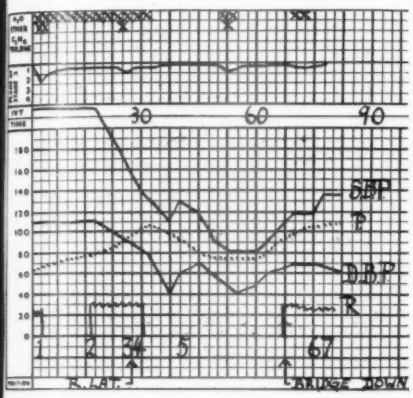

FIG. 1.—Male, 41. Lumbar sympathectomy. (1) Intubation. (2) Pentamethonium 20 mg. I.V. (3) Pentamethonium 20 mg. I.V. (4) Pentamethonium 20 mg. I.V. (5) Incision. (6) Extubation. (7) Wound closed. Although hypertensive, a large dose of pentamethonium (60 mg.) was required to lower the systolic blood pressure to 80 mm.Hg. In spite of light anæsthesia, no other relaxant drug was required, and respiration was easily "controlled" for the greater part of the operation.

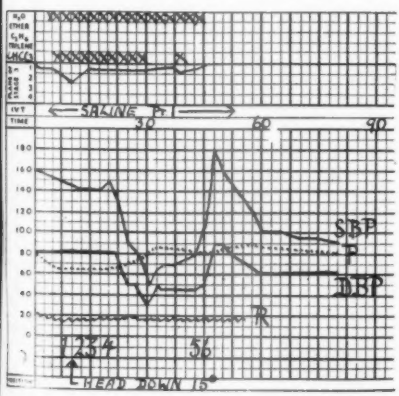

FIG. 2.—Male, 67. Millin's prostatectomy. (1) Intubation. (2) Decamethonium 2 mg. I.V. (3) Incision and pentamethonium 10 mg. I.V. (4) Pentamethonium 10 mg. I.V. (5) Methedrine 10 mg. I.V. (6) Extubation and Finis. Although not hypertensive and in a 15 degrees head-down position, pentamethonium 20 mg. reduced the systolic blood pressure to 50 mm.Hg. The first dose (10 mg.) had no effect on the blood pressure. A combination of deca- and penta-methonium was used to secure abdominal relaxation and reduction in hæmorrhage.

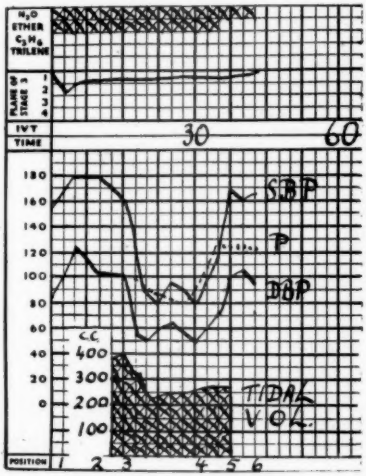

FIG. 3.—Female, 65. Recurrent hernia. (1) Intubation. (2) Incision. (3) Pentamethonium 5 mg. I.V. (4) Methedrine 10 mg. I.V. (5) Cough. (6) Extubation and Finis. Although not hypertensive and in a 5 degrees head-down position, the systolic blood pressure fell to 80 mm.Hg after pentamethonium 5 mg. Respiratory tidal volume was measured by a flow-rate meter. The pentamethonium was followed by a fall in tidal volume from 400 to 225 c.c., and raising the blood pressure with methedrine did not reverse the respiratory depression.

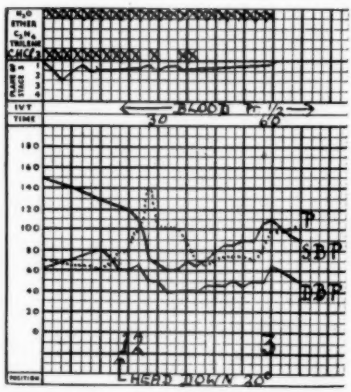

FIG. 4.—Male, 80. Millin's prostatectomy. (1) Pentamethonium 10 mg. I.V. (2) Incision. (3) Finis. Although not hypertensive and in a 20 degrees head-down position, the systolic blood pressure fell to 60 mm.Hg after pentamethonium 10 mg. There was marked "wandering" of the pulse-rate. No other relaxant drug was required.

The effect of pentamethonium may be summarized thus: (1) profound fall or postural sensitivity of the blood pressure; (2) muscular relaxation; (3) dilatation of the pupils; (4) disturbance of cardiac function; (5) respiratory depression.

It must be stressed that pentamethonium is extremely variable, both in the distribution of its action among these effects, and in the dose required to produce any or all of them.

Effect of hypotension in reducing hæmorrhage.—First, it is pertinent to ask why lowering the blood pressure should decrease hæmorrhage. That it does so is a clinical observation whether the cause be shock or hæmorrhage, or high spinal analgesia or pentamethonium. Indeed, if both spinal block and pentamethonium act by interrupting vasoconstrictor impulses, the arteriolar relaxation, by lowering peripheral resistance, should increase the flow rate and also the hæmorrhage. Such skin temperature (Milwidsky and de Vries, 1948) and plethysmographic studies (Arnold *et al.*, 1949*a*) as have been done suggest that this may be the case, at any rate in the area to which these tests have referred. The blood pressure (P), flow rate (F) and peripheral resistance (R) are linked by the formula, $\frac{P}{F} = R$ (Professor Pask, Personal communication, 1950), and it is clear from this that, if blood pressure remain constant while resistance be halved, the flow rate must double; and, equally, if flow rate (cardiac output) remain constant, blood pressure must be halved. In view of the other effects of sympathetic block, such as venular relaxation, which would lead to decreased return of blood to the heart, it seems likely that a lowering of peripheral resistance would decrease the blood pressure proportionately more than it would increase the rate of blood flow.

An important feature in the production of a bloodless field is the posture of the patient. If it be assumed that, in the horizontal person, the blood be distributed between the cephalic and caudal portions of the body in the proportion 1 : 2, it can be shown that a head-down tilt of 15 degrees will cause little alteration in the distribution of blood if the blood pressure be 200 mm.Hg; but that, if it be only 30 mm.Hg, such a head-down tilt will produce a marked alteration in the distribution of the blood, three parts going cephalwards while only two parts go caudalwards. The effect of gravity upon the blood becomes progressively more marked as the blood pressure falls; when the blood pressure is low, relatively more blood passes through the dependent portions of the body, and hæmorrhage is therefore less in the more elevated parts.

The effect of gravity will also be felt upon the venous blood, and, in the absence of heart failure or raised intrathoracic pressure, the venous pressure being low, the effect of gravity will be marked. Thus venous bleeding is also likely to be reduced by suitable posture of the patient.

Reduction in *total* blood flow may also be effected by reduction in cardiac output, due to diminished venous return and to direct action of pentamethonium upon the heart, evidence of which is to be found in electrocardiographic tracings.

The assumption has here been made that sympathetic block produces similar vascular effects in all structures, but this assumption is probably untenable; for, while it certainly produces arteriolar relaxation in the skin, as evidenced by skin temperature, there is little evidence that the same effect is produced in muscle, bone or areolar tissue. The evidence is that the vascular bed of muscle may be very different in its reactions from that of other tissues (McDowall, 1950). When assessing reduction in hæmorrhage, attention is almost necessarily directed to muscle masses. The possibility of a diversion of blood from muscle and, perhaps, other tissues must be borne in mind. In this way, the result of skin temperature tests and of the plethysmographic studies of Arnold *et al.* (1949*a*) could be understood. The latter made use of a digital plethysmograph, and showed that pentamethonium increased volume and shortened filling time, but the amount of skin in such an experiment is disproportionately large and the finger contains no muscle.

It may even be that blood flow through the kidneys is increased at the expense of the rest of the body, although such work as has been done with tetra-ethyl-ammonium bromide suggests that this does not occur (Aas and Blegen, 1949).

The hypotensive effect of methonium compounds.—It is interesting to draw a parallel between the hypotensive effect of pentamethonium and that of decamethonium. Pentamethonium usually produces a profound fall of blood pressure in the anæsthetized patient, and this effect is usually more dramatic in hypertensives. The dose required to produce a 50% fall in the systolic pressure is often as little as 5 mg., but may be as great as 60 mg. (Figs. 1, 3, 4). The duration of the effect may be anything from a few minutes to an hour. Postural sensitivity may be present for an hour or more. In some cases, no fall in blood pressure can be obtained, as in a case, recently reported by Freeman (1950), of a hypertensive girl of 16. Professor Pask (Personal communication, 1950) has suggested that she may have been one of those cases of aortic hypertension described by Wiggers (1944), and this might

account for sympathetic block failing to lower the blood pressure. Great variability in the effect of pentamethonium is sometimes to be found even in the same patient at different times (Fig. 2).

On the other hand, a fall in blood pressure after decamethonium is uncommon, but it may occur, and this fall is occasionally profound. The duration of the fall, as with pentamethonium, is variable, and postural sensitivity appears to remain for at least an hour. In one case, decamethonium having been used for endotracheal intubation, an operation lasting one hour was performed on the neck. The patient was then held in a sitting position to apply the bandage. Syncope occurred, but recovery ensued on regaining the horizontal. Not only is there a variation between patients, but the same patient may respond by a fall in blood pressure to an initial dose of decamethonium, while subsequent doses have no effect (Fig. 5).

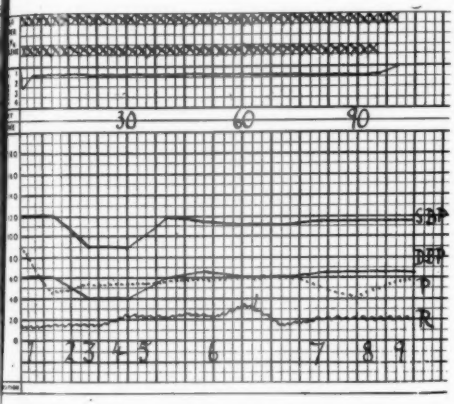

FIG. 5.—Female, 53. Cholecystectomy. (1) Intubation. (2) Decamethonium 2 mg. I.V. (3) Incision. (4) Peritoneum open. (5) Decamethonium 1 mg. I.V. (6) Decamethonium 2 mg. I.V. (7) Decamethonium 2 mg. I.V. (8) Peritoneum closed. (9) Extubation and Finis. The initial dose of decamethonium produced a 25% fall in systolic blood pressure. Subsequent doses had no hypotensive effect.

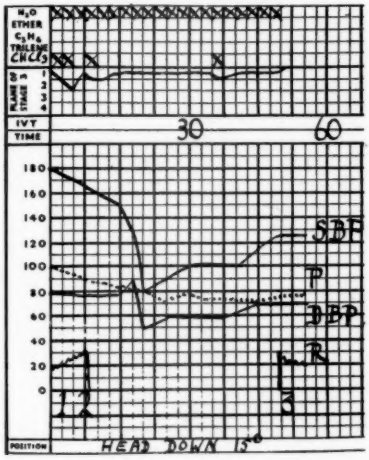

FIG. 6.—Male, 72. Millin's prostatectomy. (1) Intubation. (2) Pentamethonium 10 mg. I.V. (3) Extubation and Finis. Only N_2O was used for the greater part of the operation. Pentamethonium 10 mg. provided adequate relaxation, and respiration was easily "controlled" for nearly 40 mins.

The effect of both decamethonium and pentamethonium in lowering the blood pressure is rapidly reversed by methedrine, ephedrine or adrenaline (Arnold and Rosenheim, 1949*b*) (Figs. 2, 3).

There is thus a distinct resemblance between decamethonium in the occasional patient and pentamethonium in the generality of patients.

Muscular relaxation.—There is a form of muscular relaxation which is common, but not invariable, after the administration of pentamethonium, and use has been made of this in a number of cases, anæsthesia being maintained in the first plane of the third stage and no other relaxant drug being used. This form of relaxation is peculiar; it presents more the feature of diminution in muscle tone than of true paralysis. The relaxation persists so long as respiration be quiet, but disappears completely if coughing or breath-holding occur (Figs. 1, 4, 6).

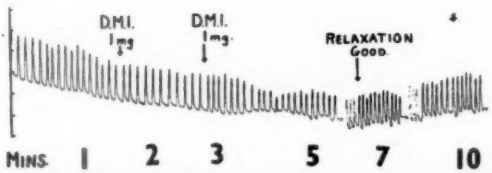

FIG. 7.—Spirometer tracing. Decamethonium 1 mg. I.V. at 1½ mins. had little effect on respiration; repetition at 3 mins. was followed by marked, but transient, depression. By 7 mins. amplitude was almost at original level, but abdominal relaxation was good.

On the other hand, with decamethonium, the first effect is true muscular paralysis, but there is great variability in the dose required to achieve this, and the occasional case is seen in which it fails to occur, even after large doses. A dose of decamethonium which produces effective relaxation of the abdominal muscles is likely also to paralyse the muscles of respiration, but the latter recover in a comparatively short time, while the abdominal relaxation usually continues for a considerable period, provided that respiration be easy. If the airway be obstructed, or if coughing or breath-holding occur, the abdominal relaxation disappears (Fig. 7).

At this point, it may be worth while to consider the effect of mephenesin ("Myanesin", B.D.H.) in producing muscular relaxation. With this drug, voluntary movement is little affected in the conscious subject, while, in the anæsthetized patient, muscle tone is reduced and relaxation is present, provided that, once again, respiration be easy. Respiratory paralysis does not occur, save for a period of seconds in certain cases in which a relatively large dose is given rapidly (Davison, 1948), and this is probably due to the high pH of the drug.

The resemblance between the action of mephenesin and of decamethonium and pentamethonium is very marked.

Respiratory depression.—Pentamethonium may cause depression and irregularity of respiration (Barnard, 1949). Furthermore, so-called "control" of respiration is very easy to establish, even in light anæsthesia, an effect which is also noticeable with decamethonium, with which drug passive ventilation may be maintained without difficulty long after paralysis of the respiratory muscles has worn off (Figs. 1, 3, 6).

Sites of action.—Thus, the pharmacological action of penta- and deca-methonium has marked similarity, although the emphasis differs. It may be imagined that there are three sites of action for these drugs, (1) at the myoneural junction, (2) at autonomic ganglia, and (3) in the spinal cord. The muscular *paralysis* of decamethonium is apparently due to action at the myoneural junction (Paton and Zaimis, 1950). The fall in blood pressure which occurs usually with pentamethonium and occasionally with decamethonium is due to peripheral vasodilatation, probably from block at autonomic ganglia. The occurrence of pupillary dilatation after the administration of pentamethonium (Davison, 1950; Enderby, 1950; Ball, 1950) may also be a sign of action on the autonomic system, which is not without interest in considering cardiac upsets, three forms of which seem to occur with this drug:

(1) "Wandering" of the pulse-rate, without any obvious changes in the electrocardiographic record; the pulse-rate may vary considerably within a few minutes.

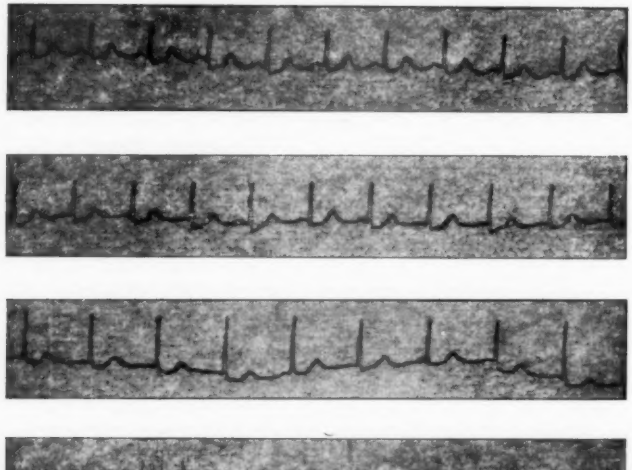

FIG. 8.—E.C.G. Tracing. *Top* (10 mins.): Some depression of S-T interval. B.P. 140/80. *2nd* (17 mins.): S-T depression more marked; P-R interval occasionally shortened. B.P. 150/80. *3rd* (22 mins.): S-T depression greater: P-R interval further decreased. B.P. 130/80. *4th* (55 mins.): Appearance generally similar to top tracing. B.P. 130/70. (Pentamethonium 10 mg. I.V. at 15 and 20 mins.—same case as Fig. 2.)

(2) Extrasystoles, alteration in the site of the pacemaker and other arrhythmias.
(3) Depression of the S-T interval, suggesting coronary insufficiency.

These effects may all be evidence of action of the drug on the autonomic system (Figs. 4, 8).

The "late" relaxation with decamethonium and the relaxation with pentamethonium and mephenesin are suggestive of action in the spinal cord. This curious state of reduced muscle tone, with little interference to voluntary movement, or, in the anæsthetized patient with little interference to respiration, may be explicable in this way. There are other reasons for assuming that mephenesin has a site of action in the spinal cord, and its action in tetanus (Davison *et al.*, 1949) is not the least of these.

In this connexion, Paton and Zaimis (1950) have shown that the action of decamethonium at the myoneural junction is similar to that of a large dose of acetylcholine; it being known that, while small doses of acetylcholine excite, massive doses depress, muscular activity. Earlier work has shown that small doses of acetylcholine augment, while larger doses depress, certain spinal reflexes, including the knee-jerk (Schweitzer and Wright, 1937; Merlis and Lawson, 1939; Bülbring and Burn, 1941). It is some reflex not dissimilar from that which produces the knee-jerk which is responsible for the maintenance of muscle tone. It thus seems possible that the "methonium" effect in producing muscular paralysis at the myoneural junction and in producing diminished muscular tone by action in the spinal cord may be due to similar mechanisms. Something of the sort may be thought to occur at autonomic ganglia, and recent work tends to show a like difference in the effect of acetylcholine on the heart (Bülbring and Burn, 1949), so that the cardiac upsets might be explicable in a similar way.

Pentamethonium as an antidote to decamethonium.—In the above circumstances, it is somewhat surprising that pentamethonium should be considered antagonistic to decamethonium. There seems to be some evidence for this (Organe, Paton and Zaimis, 1949), but the matter is not yet conclusively proved. Injection of decamethonium does not prevent hypotension on administration of pentamethonium, whatever be the effect on muscular relaxation. A combination of the two drugs has frequently been used in order to produce both relaxation and a fall in blood pressure, and the alleged antagonism does not appear to be convincing (Fig. 2).

Hazards.—The greatest danger from such drastic alterations to the circulatory system is anoxic damage to the brain, and herein lies the importance of maintaining a head-down tilt, or, at the very least, of avoiding elevation of the upper part of the body. Reference to the formula $\left(\frac{P}{F} = R\right)$ shows that a foot-down tilt of 15 degrees decreases the proportion of blood in the cephalic portion of the body from one-third to one-seventh, and it is more than likely that such a reduction in blood flow will, sooner or later, lead to disastrous consequences.

If too low a blood pressure be maintained for too long a period, there is danger of renal ischæmia. The effect of pentamethonium is rapidly reversed by methedrine, but there may be difficulty in maintaining the exact level required. It should be stressed that, provided good use be made of posture, it does not seem necessary to lower the blood pressure below 80 mm.Hg to obtain adequate reduction in capillary hæmorrhage. It had been hoped that, like spinal analgesia, pentamethonium would increase, rather than decrease the renal blood flow, but such work as has been done with a similar drug suggests that this may not be the case (Aas and Blegen, 1949).

Reactionary hæmorrhage, occurring on recovery of the blood pressure to normal, especially when this has occurred rapidly, is a possible danger.

It might be expected that cerebral thrombosis would be caused by the serious alteration in hæmodynamics, the more so because the effect of pentamethonium is very marked in hypertensives. One such case has occurred; this was a man who, although a grave risk, made a satisfactory immediate recovery from operation, but died suddenly four hours later, death being found at autopsy to be due to cerebral thrombosis.

The electrocardiographic records suggest that there is a risk of cardiac failure, either from interference with coronary blood flow or from disturbance of the conductive mechanism of the heart. In this regard, the use of methedrine, although less dangerous than ephedrine or adrenaline, cannot be considered perfectly safe, especially if the heart has been sensitized by cyclopropane, trichlorethylene or chloroform.

Disturbance of respiration is not without danger. Most anæsthetists to-day are only too familiar with complete cessation of respiration, and this would cause little embarrassment; small degrees of respiratory depression are often disregarded and herein lies danger (Fig. 3). Furthermore, since pentamethonium apparently blocks sympathetic impulses, it may be a factor in producing bronchospasm, and its use with one patient who was subsequently discovered to have been an asthmatic, was followed by death from massive pulmonary collapse. In this case, thiopentone and cyclopropane were also administered, and, as they are both parasympatheticomimetic in action, the part of the pentamethonium in producing a fatal

outcome is difficult to assess, but it is worthy of note that a similar case has been reported after the use of tetra-ethyl-ammonium bromide (Schwarz, 1949).

It should be emphasized that hæmorrhage may still occur in the hypotensive patient from injury to large vessels, and such a patient is in a poor state to react to this added burden.

Therefore, it should be said and must be clearly understood, that, while the technique of controlled hypotension displays a picture full of inviting possibilities, sinister shadows still mar the landscape, and this technique must be much more fully tested and tried under controlled conditions before its use be extended.

ABSTRACT.—Pentamethonium iodide (bis-trimethylammonium pentane di-iodide), when given intravenously to anæsthetized patients, may produce (1) profound fall or postural sensitivity of the blood pressure; (2) muscular relaxation; (3) pupillary dilatation; (4) disturbance of cardiac function; and (5) respiratory depression.

Hypotension and decreased hæmorrhage at operation seem to be associated. This may be due (1) to the greater effect of gravity on the distribution of blood when the blood pressure is low; and (2) to the effect of gravity on venous blood. Less certain factors may be (3) reduction in cardiac output due to (*a*) direct action of the drug on the heart, and (*b*) diminished venous return; (4) discriminatory peripheral vasodilatation in which the muscles (and, perhaps, some other tissues) play no part; and (5) discriminatory arteriolar relaxation in such organs as the kidney.

The effects of pentamethonium and decamethonium are compared and the variability of response is stressed. It is suggested that these drugs act (1) at the myoneural junction; (2) at autonomic ganglia; and (3) in the spinal cord. The action of acetylcholine at these sites suggests a similarity of mechanism in production of myoneural block, reduction of spinal reflex tone and, possibly, of cardiac upsets.

The hazards associated with this technique are stressed. They are thought to be (1) cerebral anoxia, especially likely to occur if a foot-down tilt be adopted; (2) renal ischæmia; (3) reactionary hæmorrhage; (4) cerebral thrombosis; (5) cardiac failure; and (6) respiratory upsets, especially massive pulmonary collapse.

Whether this technique has any place in surgery is a question which must await further trial under controlled conditions.

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Mr. F. Boyes Korkis: "Bloodless field anæsthesia" was used in 49 selected cases (Table I). In this very small series there were 4 cases of reactionary hæmorrhage (Table II). There were no general complications.

From the surgeon's viewpoint the results in the aural cases were excellent in most, though not in all. It helped greatly in the external ethmoidectomies. For S.M.R. operations a dry field can be obtained by other methods with less risk of hæmatomata, for this complication occurred in 50% of the S.M.R. cases in this series. In major neck surgery it aids materially in shortening the operation time and in reducing blood loss. It allows the performance of better surgery when the operation involves work in small, dark, deep cavities. The future may show that the end-result of fenestration surgery has been favourably influenced. It permits more complete surgery with less chance of damage to important anatomical structures in some operations (e.g. external ethmoidectomy) and it results in a saving of a considerable amount of time in long operations.

The high position of the head in fenestrations makes for awkward working angles. It is hoped that further development will overcome this disadvantage. Sometimes the method fails to ensure hæmostasis, and if the pressure returns too rapidly, bleeding may occur post-operatively, as it did with one thyroidectomy.

There should be complete co-operation between anæsthetist and surgeon in all phases of the management of a case, and it is not a technique for the inexperienced—surgeon or anæsthetist. Hæmostasis must be complete and absolute and the surgeon who adopts this method must be meticulous in the control of *all* bleeding points—no matter how small—for a trickle may become a torrent when the pressure rises. Large vessels should be ligated before their division, as large vessels will still bleed, and blood loss must be prevented, if possible. Blood loss should be made up by blood transfusion—and here the anæsthetist co-operates with the surgeon. Therefore, suitably matched blood should be available.

When "bloodless field anæsthesia" is employed by a team experienced in the technique, the surgeon gains great advantages in carefully selected cases.

TABLE I.—OPERATIONS PERFORMED SINCE MARCH 1950

Operation	Number
Fenestrations	15
Mastoidectomies	14
Facial nerve explorations	2
S.M.R.	6
External ethmoidectomy	2
Caldwell-Luc	1
Thyroidectomies	5
Laryngectomy	1
Laryngo-fissure	1
Glands of neck	1
Excision branchial cyst	1
Total	49

TABLE II.—POST-OPERATIVE COMPLICATIONS

1 thyroidectomy (Toxic Goitre treated by Thiouracil). Post-operative bleeding.
3 S.M.R. operations. Hæmatoma.
1 laryngofissure. Surgical emphysema (unrelated to anæsthesia—probably from coughing)
There have been no cerebral and no renal complications

Dr. Mita Barnes showed 4 charts out of a series of 150 cases to illustrate the reaction to pentamethonium iodide in different age-groups. This was in marked contrast to spinal block and other ganglionic blocks such as curare in which the dose of drug seemed to depend chiefly on the weight of the patient. With pentamethonium iodide age seemed to be the determining factor, though it was impossible to forecast the amount of the drug required to produce a fall in blood pressure. It may depend on the level of adrenaline in the circulation, which is higher in young people than in old, or in some other hormonic factor.

The charts also illustrated that the fall in blood pressure did not depend on the position of the patient, and all the patients in the series had been operated on in the horizontal position.

One chart showed a resection of a mandible on a man of 67 under pentamethonium iodide, in which a severe hæmorrhage from the internal maxillary artery was experienced towards the end of the operation. The patient showed no signs of shock and it was thought that perhaps pentamethonium iodide might be of value in the treatment of shock, buffering the circulation against gross trauma and hæmorrhage.

There was only one death in the series, and that was from reactionary hæmorrhage ten hours after the operation.

Dr. R. P. W. Shackleton (*Winchester*) said that he and his colleagues had experience so far of over two hundred cases without apparent ill-effects. The technique was still in the experimental stage, but results gave such attractive operating conditions that there was a danger of surgeons demanding hypotension in unsuitable cases. Taking one of the possible dangers raised by Dr. Armstrong Davison (that of renal damage) he gave figures suggesting that qualitatively there was no reduction in renal excretion even after prolonged and profound hypotension produced by autonomic ganglion block. Finally he gave details of a case, of which he had seen the notes, which had ended fatally. The patient had had an extensive neoplasm which turned out to be inoperable. Severe hæmorrhage was successfully controlled by the use of hexamethonium bromide, but the patient died two days later. No attempt had been made to raise his blood pressure which had remained between 50 and 70 mm. systolic until he died. This, combined with the use of the drug late to control hæmorrhage after some blood loss, rather than giving it early to prevent it, were two errors in technique which probably hastened the unavoidable death. Dr. Enderby had clearly indicated certain basic principles which demanded strict observance. He ended by urging the careful selection of suitable cases.

Dr. C. F. Scurr: During early trials of methonium compounds at Westminster Hospital, it quickly became apparent that pentamethonium iodide was a powerful hypotensive agent. I therefore used it successfully to control hæmorrhage in otological operations. The first reference to the use of pentamethonium iodide in this way was made in Dr. Geoffrey Organe's 1949 Presidential Address to this Section (*Proc. R. Soc. Med.*, 1950, **43**, 181).

The method was extended to a variety of operations, e.g. sympathectomy, mastectomy, thyroidectomy.

Blood pressure was checked by direct arterial manometry. These readings confirm what Enderby said about adverse effects of controlled respiration.

Optimal results are obtained with 60 mm.Hg systolic pressure, but it may fall lower and be difficult to check. In such cases, we have found valuable the cardiotachometer loaned by G/Capt. Soper. This is based on the electrocardiograph, and selects the highest voltage impulse, the R wave, causing a neon light to flash with each heart beat; pulse-rate is shown on a dial. It is a great comfort to have this continuous visual indication of a regular heart beat in these hypotensive cases.

Dr. John Gillies discussed in general terms the state of induced hypotension. He considered that the optimal level of blood pressure for the patient's safety and the surgeon's convenience was 70 mm. to 80 mm.Hg. In most operative fields, especially if advantageous posturing of the patient is possible, the difference in bleeding associated with pressures of 70 mm. and 50 mm.Hg is usually not significant. Hæmostasis is easier in ischæmic tissues but must be meticulous if reactionary hæmorrhage is to be avoided. A test dose of 5 mg. methedrine given before closure of a wound was advised as a useful measure to discover potential bleeding points. The relationship of prolonged low blood pressure to renal failure offered no problem so long as blood volume remained normal and good oxygenation was maintained. This was compared with hypotension due to hæmorrhage where anoxia arising from compensatory vasoconstriction may more readily contribute to renal and hepatic failure.

Dr. A. H. Musgrove had used pentamethonium bromide to produce hypotension in a variety of surgical procedures. It was particularly useful in laryngectomy, excision of pharyngeal diverticula, and removal of malignant glands of the neck. Mr. R. D. Owen, former President of the Section of Laryngology, was convinced that "Elective Hypotension" produced in this way had so simplified block dissection that cases formerly considered most hazardous can now be operated on, with comparative ease and comfort.

Small doses of methedrine should be given before closure to encourage bleeding so that all bleeding points may be ligated.

No posture had been used, and so far none of the dire sequelæ mentioned by Dr. Armstrong Davison had been encountered.

Dr. J. B. Wyman: At Westminster Hospital, I have now had an extensive series of cases using pentamethonium iodide. I find there are three factors which govern the initial doses.

(1) *Stability of blood pressure.*—The patient with a labile blood pressure requires a smaller dose to produce the same effect than would a patient with a stable blood pressure. The patient's reaction to pentothal serves as a good guide.

(2) *Age.*—In old patients, a small initial dose produces a profound effect. In the young, a large initial dose, plus the effect of gravity, is required.

(3) *Metabolic rate.*—In people with raised metabolic rates, a large initial dose and large maintenance doses are given.

My initial dose has varied between 20 mg. and 100 mg. and my total dose has, on occasion, exceeded 300 mg.

In order to dry the operating area successfully, it is advisable to position the patient as early as possible and I use a tilting anæsthetic trolley.

[*April* 6, 1951]

Analgesics as Supplements During Anæsthesia

By WILLIAM W. MUSHIN, M.B., B.S., F.F.A. R.C.S.
Department of Anæsthetics, Welsh National School of Medicine

GENERAL anæsthesia as known to-day consists partly of pain relief to the patient, and partly of facility of operation to the surgeon, with an overall necessity of the minimum of hazard to the patient's life and health.

Unconsciousness is still an inevitable accompaniment of general anæsthesia, since we do not yet possess a drug which, when administered systemically, depresses peripheral pain perception in a way comparable to that in which curare interrupts motor activity.

Such a drug may yet be found. Even so, because of tradition and because surgery from its earliest days was associated with the possibility and fear of death, there is a widespread public demand for unconsciousness for its own sake. When unconsciousness is present freedom from pain is assumed.

Anæsthetists are faced with two problems: first, the provision of unconsciousness and second, the obliteration of reflexes set in motion by the operation which, if unchecked, would cause either actual movement, or tight muscles, or harmful effects on the circulation and respiration.

General anæsthesia produced solely by such drugs as ether or the intravenous barbiturates is not the answer to the problem. These drugs, apart from depressing the whole of the central nervous system to a greater or lesser extent, also derange in varying degrees the function of all other organs. Such anæsthesia has aptly been termed "depression anæsthesia"; and it is unlikely that a single drug of this kind will ever make the perfect anæsthetic.

For many years now the tendency has been to use small doses of general anæsthetic to place the patient just below the level of consciousness, leaving no memory of pain. Reflex activity arising from the operation is prevented by other means which neither depress the central nervous system nor interfere with the activity of the vital organs. Such a technique is exemplified in the combination of light anæsthesia with nerve block or the use of light anæsthesia with spinal analgesia. Very remarkable and strikingly good results were obtained with these techniques up to the advent of curare. This drug altered the whole picture practically overnight. Here was a means of obliterating reflex activity without affecting to any extent any part of the body other than the myoneural mechanism, the only real disadvantage being the inevitable paralysis of the respiratory muscles. Curare combined successfully with every general anæsthetic, but it was easier to maintain light anæsthesia by certain anæsthetics. Nitrous oxide-oxygen was an obvious choice, in view of its well-known freedom from side-effects provided that the oxygen percentage is adequate. It soon became clear, however, that a combination of nitrous oxide and oxygen and curare gave adequate relaxation only when the respiration had ceased or was very poor. Augmentation of breathing by the anæsthetist was nearly always required. The custom then gradually arose of adding a little of the more powerful anæsthetics such as ether, trilene or thiopentone in order to produce slightly deeper anæsthesia than can be provided by nitrous oxide-oxygen alone. Here, a part of the relaxation is produced by the anæsthetic and the rest by the relaxant, and full relaxation is obtained without inducing apnœa. The dose of general anæsthetic to use with a relaxant became not that which just kept the patient asleep, but rather that which made the relaxant safe.

A favourite drug even now for supplementing nitrous oxide and oxygen is thiopentone. A technique of administering small intermittent doses of thiopentone in this way has been described by Gray (1948) and in skilled hands gives very good results indeed. It is not uncommon, however, to find that a long operation conducted on these lines requires the use of comparatively large doses of barbiturates, and a prolonged recovery period may result.

For some years pharmacologists as well as anæsthetists have stressed the point that the barbiturates, whilst they are excellent hypnotics, have little effect on pain sensibility unless given in what is virtually overdosage. It seems wrong, therefore, to use a barbiturate in order to subdue reflexes arising from pain stimuli. One could give many examples illustrating the unsuitability of barbiturates to prevent pain but I will merely direct your attention to an everyday observation: when we administer intravenous thiopentone for a simple operation in the casualty department we know that immobility can only be promised at the cost of deep respiratory depression. It is during the period of apnœa that the abscess can be incised or the finger nail removed, without movement by the patient. Only recently a small spirometer was described by which the administration of thiopentone could be related to respiratory activity: as soon as this instrument showed increased respiratory activity more thiopentone was indicated.

If, therefore, a supplement is to be administered to reinforce nitrous oxide-oxygen and to make more safe the use of relaxants, it would seem that this supplement must have a specific depressant effect on pain. I first saw analgesics used in this way in San Francisco two years ago. The remarkable effects produced in the operating theatre by Dr. W. B. Neff and the striking post-operative recovery of his patients induced me to make further investigation of the principles involved. The drug I have mainly used has been pethidine, though I have tried a variety of other analgesics, morphine, heroin, Physeptone, Heptalgin, codeine and a new, promising synthetic known as Ciba 7115 or Cliradon. The first four of these, i.e. morphine, heroin, Physeptone, Heptalgin, depressed the respiration very markedly and were soon abandoned. The others, and particularly the last, were all as satisfactory as pethidine. I have only continued with this drug simply because no method of determining which is the better drug has so far been evolved, though we hope later to be able so to do.

My experience, therefore, is based mainly on the use of pethidine; I do not mean, however,

to imply that this is the only, or even the most suitable, analgesic for anæsthetic purposes. Although its analgesic potency is high compared with its depressive effect on the respiration, that effect is definite and may be marked if the drug be injected intravenously in too large doses or too rapidly.

Hitherto, in medical and obstetrical practice pethidine has usually been given by mouth. In anæsthesia the drug is injected intravenously and our ideas of dosage must be readjusted. By vein, 25 mg. is an effective single dose and if more should be given, it may induce apnœa.

This fact alone may account for the reports of a so-called "idiosyncrasy" to pethidine. The respiratory depressive effect of pethidine is markedly enhanced when either morphia or a barbiturate or a combination of the two has already been given, while the effects of anæsthetics such as ether are strongly potentiated by pethidine. In one case a robust man after a pre-operative injection of morphia received 0·5 gramme of thiopentone: ten minutes later 50 mg. of pethidine were given intravenously: breathing promptly ceased and was not resumed for nearly three-quarters of an hour, by which time the hernial repair was nearly complete. On the other hand when no previous depressants have been administered a comparatively large amount of pethidine may be given slowly and in dilute solution without dramatic effect on the breathing. This has been reported by Dr. Henning Ruben of Copenhagen (1951). He showed—and our experience confirms the observation—that as much as 100 to 150 mg. of pethidine in 1% solution may be administered intravenously if injected with extreme slowness, the only effect being slowing of the respiration and a general drowsiness. When the patient's respiration has slowed down to 10 per minute the laryngeal reflexes are sometimes so depressed that laryngoscopy and intubation are possible.

Before describing the routine administration of pethidine in anæsthesia I must refer to another grave problem which confronts us in these days of relaxants. I refer to the need for ensuring that the patient really is unconscious when subjected to large doses of relaxants. Our pharmacological colleagues warned us long ago of the possibility that the patient might be awake during operation. Cases have already been reported of this untoward state of affairs and I came across one definite instance in my own department. In the middle of a pneumonectomy on a middle-aged female patient the anæsthetist had referred to her as a "tough old bird". The next day this particular patient expressed her strong disapproval of the description. I am inclined to believe that this occurrence may be more common than we think. It is clear that with the present-day large doses of relaxants little objective evidence is available for the anæsthetist to determine the presence or absence of unconsciousness. A patient who is motionless may be conscious but curarized, while one who kicks may be unconscious and acting reflexly. The first patient needs anæsthetic, the second relaxant. It seems to me, therefore, that we must administer doses of anæsthetic and analgesic which, from our previous experience of these drugs in the absence of relaxants, we believe to be adequate to ensure unconsciousness. On to this background the administration of relaxant must then be made. More or less by experiment and observation I have come to the conclusion that if an average healthy adult receives a preliminary injection of morphia, then is given say 0·25 to 0·5 gramme of thiopentone followed by 30% oxygen and nitrous oxide, he will remain asleep and unresponsive to mild stimuli for perhaps only half an hour. If immediately after the administration of the nitrous oxide-oxygen he is given 25 to 50 mg. of pethidine and this is repeated once every half-hour, the anæsthesia may be continued for many hours and the patient will remain unresponsive to all but powerful stimuli. This is the background that I have adopted. The relaxants are used as an added measure to subdue powerful reflexes or to depress or abolish respiratory activity.

TABLE I

PETHIDINE (Synthesized 1939)		
		Meperidine HCl (Britain)
		Isonipecaine, Demeral (U.S.A.)
Strong	.. ..	Morphine-like (analgesia)
Moderately strong		Papaverine-like (relaxes bronchi, intestine, uterus, vessels)
Weak	.. ..	Atropine-like (anticholinergic, suppression of saliva, tachycardia, &c.)
		Antihistaminic

Table I is a summary of the main pharmacological actions of pethidine.

It can be seen that pethidine has a weak atropine-like action, producing both dryness and moderate tachycardia. The pupils, however, are invariably small during its use in anæsthesia. It has a more powerful papaverine-like action and this accounts for its analgesic effect on pain arising from spastic viscera. Since the pain of surgical operations is rarely of this sort, future objective analysis of analgesic action may well alter our ideas as to the suitability of pethidine for our purpose.

TABLE II

	Respiratory depression	Effect on B.P.	Analgesic potency	Hypnotic effect
Ether	–	–	++++	++++
Morphine	++++	Slight fall	++++	++
Pentothal	++++	Marked fall	–	++++
Procaine	Sudden apnœa	Sudden fall	++++	++
Pethidine	+	–	++++	+

Table II compares a number of drugs, each representing a class, which have been used to supplement nitrous oxide. Since the ideal drug for this purpose will have a high analgesic potency with little other action, the drawbacks of each are readily visible.

In most major surgery, the anæsthetic procedure we adopt is as follows: As premedication the usual combined dose of morphia and atropine is given. Anæsthesia is induced with little more than the dose of thiopentone necessary to put the patient to sleep. If intubation is to be performed, a relaxant is injected at this time and pure oxygen given until full relaxation has developed. Nitrous oxide with about 30% oxygen is now administered. Either a diaphragm needle is inserted into a vein or, better still, an intravenous drip is established. Easy means of injection into a vein is essential and if it is not achieved, the method should be abandoned or recourse made to the variation mentioned later.

The first dose of pethidine is now injected intravenously, the amount depending on the robustness of the patient. A healthy adult receives 50 mg. while weaker individuals get 25 mg. Time, usually up to a quarter of an hour, is allowed for stabilization of the nitrous oxide-oxygen anæsthesia before starting the operation. In fit patients another 25 mg. of pethidine may possibly be injected within a quarter of an hour of the first dose, but this is not usually necessary.

This basic combination of nitrous oxide-oxygen and pethidine is now continued throughout the operation. Repeat doses of pethidine are given about every half an hour, each repetition being 25 mg. in the average case. Both the intervals and the dose are varied slightly according to the patient's age and physique. These further doses of pethidine are given even in the absence of any clear signs that the patient is coming round, particularly in the early part of the anæsthesia; for signs of recovery may well be masked by the relaxant.

Should there be any reflex activity of the patient, whether it be movement of a limb, coughing or tight muscles, tranquillity is restored by administering a relaxant. The more relaxant that is used the more depressed will be the respiration, and the more likely the necessity of assisted respiration. When pethidine and nitrous oxide are administered without relaxants the respiratory volume is generally satisfactory, though the rate may be rather slow.

Reference has already been made to another method of using pethidine, one which is now under active investigation. In this method the initial thiopentone is omitted and a 1% solution of pethidine is made up and injected with extreme slowness, each 10 mg. of pethidine taking perhaps five to ten seconds. This continues until the respiratory rate is down to about 10 or 12 per minute. The average adult requires about 100 to 120 mg. to reach this point. The patient is now obviously very drowsy and euphoric. Nitrous oxide and oxygen are administered and are found to produce a tranquil anæsthesia for most extra-abdominal surgery. The method is very useful in cases of short duration as it allows of rapid recovery of consciousness.

When good veins are absent, the pethidine, and indeed the relaxant too, may be given intramuscularly, 100 mg. of pethidine injected in this way providing a depot from which adequate absorption will occur. Such an injection should be made as soon as the patient is asleep or even before.

Solutions of pethidine and thiopentone are incompatible. A heavy precipitate is formed when they are mixed, and if a diaphragm needle is used the thiopentone must first be washed out with saline before the pethidine is introduced.

Dental surgery.—A preliminary intravenous injection of about 10–15 mg. of pethidine will ensure an easy and tranquil nasal gas administration and will obviate the post-operative drunkenness which sometimes follows the use of thiopentone.

Thyroid surgery.—After the sleep dose of thiopentone and the initial intravenous dose of 50 mg. of pethidine a further 50 mg. given intramuscularly will serve to maintain an even level of anæsthesia throughout one to one and a half hours of surgery. At the end of operation the patient will generally be able to talk at the request of the surgeon.

Neurosurgery.—I have only used pethidine for three neurosurgical cases. My colleague, and late assistant, Dr. D. Mansel-Watkins, who has used the method for a large number of cases, informs me that pethidine enables nitrous oxide to be administered for long periods of time without the otherwise occasional unexpected return of motor activity or coughing

on the tube, which accompanies the use of nitrous oxide alone. Intracranial pressure is not raised and bleeding is noticeably less.

In very long cases such as occur in thoracic surgery and in neurosurgery, a cumulative effect of pethidine undoubtedly occurs. After the first one and a half hours the interval between the increments of pethidine must be prolonged; otherwise the patient may be unduly depressed at the end of the operation. Should rapid recovery be required at the end of a long operation, no pethidine should be given during the last half-hour.

In major abdominal and thoracic operations the use of pethidine has given such remarkably good results that the surgeons in our area now expect its use as routine. The results are good in the sense that the surgeon is given all he desires, a quiet operating field, and an unstimulated circulatory system; whilst the patient awakes almost immediately after the operation in an analgesic state, and, though conscious, will be entirely co-operative. Amnesia as regards this immediate post-operative period is usually complete. In all cases in which we use a relaxant we administer atropine at the end of the operation, followed, after an interval, by neostigmine. In view of the atropine-like properties of pethidine, smaller doses of atropine may be used.

Our practice of giving neostigmine as routine after Flaxedil or curare is based on our personal observations on volunteers whilst methods for assessing the potency of these drugs were being worked out. We constantly found that even though the main muscular power had returned, subjective weakness persisted for many hours. It could, however, be abolished immediately by an injection of neostigmine.

All our patients wake in the theatre. This in itself is not necessarily desirable, but it does imply a safe airway, with active coughing, and general bodily activity. Amnesia and analgesia are marked and very little post-operative sedation is required. We have not seen any untoward reactions from the use of this drug, save respiratory depression when too large a dose has been injected too quickly. This is particularly liable to happen immediately after the injection of thiopentone. We have no hesitation in assisting respiration when it seems indicated, and have never attempted to reinforce the action of nitrous oxide by cutting down the oxygen. These two facts may explain our immunity from ill-effects.

Since I and my colleagues began to use this technique as a routine two years ago, no death attributable to the method has occurred. Whilst it is no method for the inattentive anæsthetist, we have had remarkably little anxiety during its use. Well-trained juniors quickly pick up the method and we can ascribe to it a degree of flexibility equalled only by cyclopropane.

The use of this combination in thoracic surgery has already been described elsewhere (Mushin and Rendell-Baker, 1950), and in this type of surgery, the flexibility, rapidity of recovery and return of cough reflex, absence of cardiac irregularities, and absence of explosion risk, are points of particular value.

The ages of our patients have ranged between 4 years and over 80. For children, we take 10 st. as being an average adult weight and estimate the fraction of the adult dose accordingly. A 5-st. child, instead of receiving a repeat dose of 25 mg. of pethidine, receives only 12 mg. Pethidine solutions do not appear to be irritant to the vein and we have seen no severe thrombophlebitis. Post-operative vomiting, while not entirely absent, has been uncommon. The liveliness of the patient from the moment of his return to bed has made severe chest complications rare. Early ambulation is easy to institute should it be desired.

Thus there is put before you a principle of using analgesics to supplement the weak anæsthetic properties of nitrous oxide, a new conception of the "anæsthetic cocktail". It is based on what might be called armchair reflection and the practical results have so far confirmed the soundness of the principle. If an analgesic were discovered which when injected into a vein gave pain relief by acting wholly on the peripheral receptors and which had little or no effect on the central nervous system, we would be very much nearer to the ideal anæsthetic combination. If the pain impulse were obliterated the need for relaxants would be reduced, the side-effects of depression anæsthesia removed and new standards in post-operative recovery established.

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Section of Neurology

President—W. Russell Brain, D.M., P.R.C.P.

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DISCUSSION ON SOME LESS COMMON CEREBROVASCULAR DISEASES

Dr. J. Purdon Martin: *Angiomatous malformations.*—These constitute a progressive and very fatal disease, the frequency of which has been revealed by arteriography and which has now become amenable in many cases to surgical treatment. Practically all of the angiomatous structures that occur in the cerebral hemispheres are arteriovenous racemose aneurysms—that is to say that instead of a capillary bed, a tangle of blood vessels is interposed between the arterial and venous systems; the arteries feeding this tangle are hypertrophied and dilated, and the veins draining it are dilated and pulsating and they contain arterial blood. Now this tangle is a monster—a baneful fate—that constantly threatens the patient's life, and eventually destroys him. It consists of vessels of an abnormal and largely undifferentiated structure, which give way from time to time until one day the hæmorrhage overwhelms him.

As most of the arteries enter the brain from the surface these angiomata typically appear on the surface, and extend in a sector, often with a roughly pyramidal shape, deeply into the hemisphere and may reach to the ventricle.

It is generally agreed that the post-mortem appearance, with the vessels emptied of their blood, gives a very inadequate idea of what the formation is like during life.

It is a very remarkable fact that although these masses must be present, though perhaps not at their full size, from birth, they give no indication of their presence until things begin to go wrong. Cerebral tissue is found between the vessels of the mass and the cerebral tracts evidently pass through it without being affected. In one of my cases the angioma was situated in the right occipital lobe, but there was no indication that it ever gave rise to any disturbance of the visual field until the day when overwhelming hæmorrhage occurred from it.

There is fairly good evidence that the incubus gradually enlarges. We know that similar formations in other situations, e.g. involving the scalp, enlarge in the course of years. Olivecrona and Riives (1948) have described a case in which arteriography was performed on two occasions with an interval of ten years between them; the films on the second occasion indicated a very large angioma and the vessels feeding it had apparently increased considerably in size. (But this evidence is not conclusive as the appearances may vary in different stages of the arteriogram.) The process by which it enlarges is, of course, not definitely known, but it seems unlikely that it is at all comparable to the process of growth in tumours. The formation expands, rather, as a physical reaction to the pulsation, i.e. the changes in pressure of the blood passing through it; and the changes that occur in its vessels, and even the formation of new vessels are probably merely reactions to the physical conditions. As it enlarges it draws more blood to itself. If new vessels form they are of a very nondescript type anatomically. What is more likely is that there is an extension towards the venous side and Cushing and Bailey (1928) have some interesting remarks on the process of arterialization that occurs in a vein into which arterial blood is diverted—the vein reacts to the pressure by thickening and the development of muscular tissue in its wall.

Although *venous* angiomas have been described it is certain that most of them are arteriovenous—even though it may be impossible to discover in the structure any vessel that can be said to have definite arterial structure. The vessels composing the tangle are very irregular in size and, at any rate, when they come to microscopic examination, most irregular in outline. Their calibre may be 3 mm. or much less or more. For the most part they have thin walls, but the walls are very irregular in thickness; they are mostly composed of fibrous tissue but there is a varying amount of muscular tissue, completely irregular in its distribution. The vessels are simply vascular channels of very imperfectly differentiated structure. It is unusual to find any elastic tissue in their walls, and if it does appear, it, again, is very imperfect. Irregular short wisps of elastic tissue may appear here and there in the wall of a vessel, or the elastica may be reasonably well developed in one section of the wall and very imperfect elsewhere. Thickenings of the intima are common and here and there a vessel may appear almost occluded. Evidently calcification sometimes occurs in these vessel walls and Cushing and Bailey (1928) figure a case, but speaking generally I think it is more likely that the

calcification which is occasionally seen in the X-ray films of cases of angioma is deposited after hæmorrhage has occurred and is laid down more in a clot than in vessel walls. Cushing mentions a case in which a presumptive diagnosis of tuberculoma was made.

(Lantern slides were shown illustrating six recently observed cases.)

These monsters threaten the lives of the patients by hæmorrhage and the hæmorrhage may be indifferently either intracerebral or extracerebral (i.e. subarachnoid) or both. It may occur at any age; one of my patients had a severe intracerebral hæmorrhage at the age of 11; another had undoubtedly had one some considerable time before I first saw him when he was 12; another patient is said to have had an illness at the age of 3 in which she was unconscious for a fortnight. On the other hand, one of the patients, of which I have shown you a section, died from the effects of her first hæmorrhage at the age of 45; as far as we were able to ascertain she had never previously had any symptoms whatever. Some later ages of onset have been recorded but the great majority of the patients have symptoms within the first three decades. In many cases fits of some kind, local or general, have preceded signs of hæmorrhage, and sometimes occasional fits occur over many years. More frequently local fits occur, and in association with these weakness develops more or less gradually in the limbs on one side of the body. The most typical symptom, of course, is the bruit. It has been present in most of the recognized cases that I have known of, and is only occasionally completely absent; it may be audible all over the head or only over the carotids. Olivecrona and Riives (1948) do not consider it a very constant sign and observed it in only 8 cases out of 42. Headaches are common and occasionally are of a typically migrainous type and associated with vomiting. In other cases they are associated with a feeling of stiffness in the neck and are suggestive of slight leakage from the aneurysm. I have, however, encountered one or two instances of a progressive severe migraine syndrome leading on to fits or unconsciousness in which arteriography has failed to reveal any suggestion of an angioma.

The only available effective *treatment* for these cases is surgical. X-ray treatment has been tried and possibly in some cases it brings about some shrinkage of the abnormal formation, but there is no conclusive evidence that it has any real effect. The radical treatment of these cases by excision is an interesting instance of the advance of neurosurgery for Cushing and Bailey wrote twenty years ago: "It is inconceivable that an angioma arteriale with its huge and well concealed feeding arteries could be successfully attacked." They had not foreseen the power of the coagulative technique.

Similar structures in brain-stem.—Similar formations occur in the brain-stem and in some instances, at any rate, the clinical course is very similar to that of disseminated sclerosis. In the early days of the war I ventured to suggest this diagnosis in one case, and it was confirmed four or five years later.

The patient, whom I first saw in March 1940, was aged 39, a highly intelligent man, an author and a well-known broadcaster. He had been well until a certain Tuesday in the previous November, when he had an attack of vomiting. The following day he felt generally weak and on the Thursday he had some difficulty in swallowing and his doctor said that his voice had a "toneless" quality. An interesting point is that a month before this onset, the patient consulted his doctor because he thought that his enunciation was slurred. The difficulty in swallowing lasted for weeks, and his voice was husky and more or less lost: a laryngologist found that the left vocal cord was paralysed. When the patient began to get up he became aware of a slight loss of power in his right hand and could not write properly, but gradually his unusual and rather pedantic handwriting was restored. At a later period he felt some heaviness of his legs in going up stairs, and he also had some tendency to giddiness. At my first examination the most pronounced sign was a slurring dysarthria; the palatal arch was narrower on the left and there was slight weakness of the left lower face; the voice seemed normal; there was also slight weakness of the right hand, and at that time no ataxia. The tendon-jerks were a little greater on the right side and a weak extensor plantar reflex could be obtained on the right foot; the right abdominal reflexes were less than the left and pin-prick and scratch were more uncomfortable on the right side of the trunk than on the left. The cerebrospinal fluid was normal. After this the patient made steady improvement for about a year, but his articulation remained imperfect, and power in his right hand was not fully restored. In February 1941, i.e. sixteen months after the onset, he had an aggravation of his symptoms; he felt completely exhausted, had photophobia, his right eye partially closed, his articulation became moderately worse, his right hand became weaker, and he had a little weakness of his right leg, and he stumbled easily. Whereas immediately before this he had been able to walk ten or twelve miles a day, he found himself unable to walk more than a few hundred yards. By March he had made some recovery from these symptoms. His articulation was then developing a staccato quality. With extreme deviation of his eyes to either side he had a little nystagmus. He had slight retraction of his eyelids with intent fixation, and in smiling there was slight overaction of the right side of his face. The degree of weakness in the right hand was much the same as before and co-ordination was not perfect. Again he made a very fair recovery and had a remission lasting three months, and then he became aware that his left hand was affected, and within a month both hands were worse than the right one had been originally. Six months later the patient wrote that he seemed so much recovered that he

began to live a more nearly normal life. I confess that his condition and the course of his illness were so much like those of disseminated sclerosis that I wavered in my diagnosis. After a further year of frequent small setbacks the patient died from a hæmorrhage into the pons and upper part of the medulla. Post-mortem examinatiion revealed a hæmangioma which occupied a portion of the left half of the pons and upper medulla.

As I have emphasized in regard to the hæmangiomata in the cerebral hemispheres, there were no indications of any deficiency until symptoms of hæmorrhage occurred and one must conclude that originally the nervous structures were intact among the abnormal vessels.

In another case, in which the patient was a woman aged 49, there were similar aggravations and remissions, and the case was regarded as one of disseminated sclerosis. The symptoms began with ataxia in walking, followed by feelings of giddiness, slight nystagmus and dysarthria. From these disturbances the patient at first made a good recovery but afterwards they recurred. After a second recurrence there were some signs of raised intracranial pressure, and the patient died following an exploration of the posterior fossa. Post-mortem examination revealed a bunch of abnormal vessels which crossed the front of the pons and passed back along the middle cerebellar peduncle; within a large part of the brain-stem there was a venous cavernous dilatation. This case occurred before the days of arteriography.

It may be that arteriography will be able to demonstrate some of these angiomata in the brain-stem, but that so far has not happened in any of my own cases. The possibility of the presence of such a formation should be considered when symptoms indicative of a brain-stem lesion come on abruptly, or when the signs of activity of a lesion which seems more or less limited to the brain-stem are intermittent.

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Professor P. C. P. Cloake: *Temporal arteritis.*—Though a comparatively rare disease many cases have been reported since it was first clearly defined in 1932, and although the name then given has persisted it is now known to involve many other arteries—the aorta itself and its primary and secondary branches but not smaller visceral vessels as is the rule in polyarteritis nodosa.

The temporal, occipital and retinal arteries are frequently attacked, but I have found no description of similar lesions in cerebral vessels, though they may show numerous ante-mortem clots and associated small softenings.

It is a disease of the elderly, and attacks both sexes equally.

It is a subacute inflammatory process of unknown causation, which undergoes resolution or termination by fibrosis often after the vessel has been occluded by clot. Recovery is the rule in spite of the advanced age of many victims.

The arterial disease is widespread and there is also widespread pain and tenderness in the limbs, back and head of such severity as to render sleep difficult and movement a torment. The patient's condition is one of great suffering and misery. The most prominent symptom is severe pain in the fronto-temporal and occipital regions with tenderness so great that the patient cannot lie in comfort with the head resting on a soft pillow and the head is usually kept protected by a shawl. This is due to involvement of the temporal and occipital arteries in the inflammatory process, a condition which at the height of the disease is apparent on inspection of the temporal arteries which are thick, tender, and often pulseless and stand out on the forehead in the centre of reddened skin which occasionally becomes centrally ulcerated by the extension of inflammation into it. Rarely, more extensive scalp ulceration and sloughing occur.

The inflammation in this visible site lasts for several weeks before it dies down leaving a hard thick artery which may still pulsate or may be pulseless.

There is, in about one-half of the cases, an involvement of the retinal arteries causing severe impairment of vision, transitory or permanent, in one or both eyes. Papillœdema, narrowing of the fundal arteries and retinitis may be seen and later optic atrophy develops in such cases.

Diplopia and strabismus have been recorded and the pupils may be dilated, irregular or unequal, and sluggish or inactive to light.

In addition there are usually general symptoms of illness often for many months before temporal arteritis appears, such as general lassitude, weakness, anorexia, wasting, mental depression, aching and tenderness of muscles and joints, neuropathy in the limbs sometimes with loss of reflexes, pyrexia, and night sweats. Mental disturbances, rarely severe, may occur and are recoverable. Signs of organic nervous lesions are exceptional and then slight and transient. One of my patients developed signs of myelitis with severe but rapidly improving paraplegia and corresponding sensory disturbance, during the temporal arteritic stage, but this is unique.

FIG. 1.—Temporal arteritis. Low magnification.

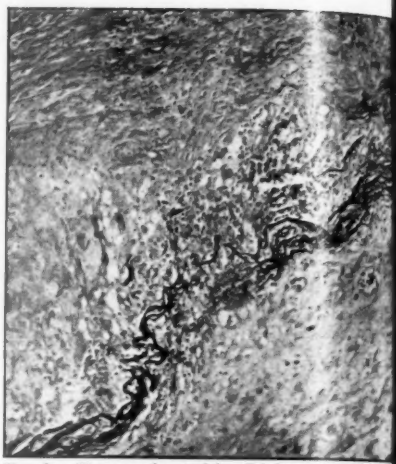

FIG. 2.—Temporal arteritis. Right vertebral artery. Elastic stain to show fragmentation of elastic laye

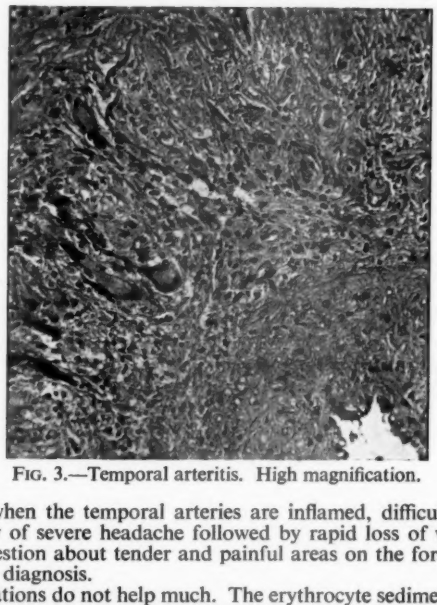

FIG. 3.—Temporal arteritis. High magnification.

Diagnosis is easy when the temporal arteries are inflamed, difficult or impossible until they are. The history of severe headache followed by rapid loss of vision in one or both eyes will lead to a question about tender and painful areas on the forehead and may guide one to a retrospective diagnosis.

Laboratory examinations do not help much. The erythrocyte sedimentation rate is usually considerably raised and falls slowly as the disease dies down. C.S.F. protein may be raised up to 300 mg.% but the fluid is usually normal in all respects. Hypochromic anæmia of moderate degree is the rule.

Pathology.—No lesions but those of blood vessels—and the results of obstruction of such vessels—are to be recognized as parts of this disease. Arteries are almost solely involved but occasionally thrombosis of large veins has been recorded during the illness.

The arterial lesion has been found not only in temporal, occipital and retinal arteries but in the aorta, carotid, cœliac, mesenteric, renal, femoral, coronary, and radial arteries.

The course of the disease in the affected arterial wall appears to be as follows. First there is slight adventitial inflammation followed by focal necrosis in the media and the spread of inflammation into the media which is converted into agranular tissue with destruction of muscle cells and breaking up of the internal elastic lamina (Figs. 1 and 2). Just external

to the broken up elastica new elastic tissue then forms and simultaneously multinucleate giant cells appear (Fig. 3). Inflammation does not spread into the intima but gross thickening of this layer occurs and the lumen becomes narrowed and often thrombosed.

The inflammatory process is subacute or chronic and spreads longitudinally along the vessel wall, never forming aneurysms or bursting.

No micro-organisms have been found in these lesions or cultured from them.

Treatment.—Relief of pain follows surgical division of the inflamed arteries and recently improvement has been attributed to the use of aureomycin.

Cerebral Thrombo-angiitis Obliterans or Endarteritis Obliterans

Cerebral thrombo-angiitis obliterans may exist as part of a widespread affection of vessels including those of the limbs, heart, stomach, kidneys, and pancreas, or it may exist alone.

In 500 cases of peripheral Buerger's disease evidence of a cerebral vascular lesion was found in 2%. In many cases of cerebral Buerger's disease symptoms and signs of the same disease in the legs have been recorded.

Affection of arteries in the limbs may occur before or after the appearance of the cerebral arterial lesions.

Ætiology.—As in the case of the peripheral disease almost nothing is known of the causes of cerebral thrombo-angiitis obliterans. If vascular spasm initiates the organic changes in the arteries, no cause for the spasm is known. It is predominantly a disease of middle age, especially of the fifth decade, and the predominance of males among its victims is very marked (as in the peripheral form).

There is no known relation to hypertension or arteriosclerosis, no racial factor, and no association with preceding or concurrent infection.

Excessive use of tobacco is common among its victims but is certainly not always found.

The case which might be called typical comes to hospital complaining of symptoms, usually sudden in onset and progressive in degree and variety over a period of weeks or months. These symptoms and signs are predominantly of cortical type: focal or generalized fits, hemianopia, hemiparesis, monoparesis, cortical sensory disorder, motor or sensory aphasia, alexia, agraphia, agnosia. Mental disorder sometimes occurs, memory defect, emotional changes, intellectual impairment, and even severe psychotic disturbance, have been recorded. Cerebral tumour is suspected and the suspicion may be strengthened by finding papillœdema.

But on tracing the history through from the earliest manifestations it will be found that not only did some of the existing disorders at first remit and relapse before becoming fixed but that further back still (perhaps five or ten years ago) were symptoms less definite and less severe but almost regularly present and so of value in diagnosis. These are paroxysmal headache or typical attacks of migraine, with or without transient focal features such as hemianopia, amblyopia, hemiparesis, aphasia or paræsthesia, transient neurasthenic states (fatigue, forgetfulness, strange cephalic sensations, &c.).

Thus, after a long period of months or years of rather vague prodromal symptoms, comes a period of transient recurrent and remitting symptoms of sharper delineation, especially symptoms arising from cortical dysfunction, and these become finally established and fixed, and the patient moves gradually into an increasing mental and physical disablement.

In a minority of cases a clue to the nature of the cerebral lesion is provided by a history of recurrent thrombophlebitis in the extremities, vasospastic and cyanotic states in the hands, or of symptoms of arterial obstruction in the coronary or tibial arteries, as in a case of my own where intermittent claudication first appeared, later coronary thrombosis, and months later transient then permanent hemiparesis.

On examination the signs of nervous dysfunction correspond to the symptoms present and there may be helpful evidence of peripheral arterial obstruction or of electrocardiographic abnormality. But the cerebral disease may precede the peripheral and cardiac. Cerebrospinal fluid changes are not usually great. A rise of pressure sometimes encountered will tend further to deepen the suspicion of cerebral tumour. Pleocytosis, sometimes partly polynuclear, and concomitant or dissociated increase of protein sometimes occur.

Radiological examination reveals nothing but occasional homolateral displacement of a calcified pineal gland but pneumoencephalography may show the lateral ventricle enlarged on the affected side and widening of sulci with increased collections of air over the cortex. Cerebral angiography is of special value revealing local narrowing or obliteration of main arterial trunks or of their smaller branches.

Pathology.—The lesions of the cerebral blood vessels may involve the internal carotid artery, the main cerebral vessels, or their smaller cortical branches.

Lindenburg and Spatz (1939) examined the cerebral vessels in 20 cases of cerebral thrombo-angiitis obliterans and classified their findings in two groups: (1) 6 cases of extensive malacia in the area of one or several large arteries—chiefly limited to one hemisphere and predomi-

nantly in the cortical area. (2) 14 cases with lesions of the type of granular atrophy of the hemisphere localized in the border zones between the three main arteries of the hemisphere—only the distal portions of which showed the changes of thrombo-angiitis obliterans. These lesions occurred in both hemispheres and showed symmetrical extension.

In some cases of both types there was thrombosis of the internal carotid artery as well as the above changes.

The cerebral arteries affected by the disease are seen mainly on the convexity of the brain as hard, white, worm-like obliterated vessels (Antoni, 1941; Davis and Perret, 1947; Luers, 1942).

Descriptions of affection of cerebral veins are very scanty. Venous thrombosis is occasionally described.

Buerger's description of the disease in the vessels of the limbs was of an acute process regarded by him as an inflammation in which all coats of the vessel, especially the media, are infiltrated with leucocytes, and later new vessels develop in the media and fibrous tissue in the perivascular region. The lumen is filled with red clot, containing foci of leucocytes and giant cells, which later organized and canalized.

Very different is the description of the histology given by Scheinker (1944, 1945) in *cerebral* thromboangiitis obliterans; so different, indeed, as to raise a doubt as to the identity of the cerebral disease with that described by Buerger. Scheinker states that the cerebral vascular changes are confined to medium veins and smaller arteries and that a primary necrobiotic stage is followed by a proliferative one. The earliest change he found was an intramural hæmorrhage in the subendothelial tissue between intima and muscularis which was then replaced by fibroblastic reaction causing great thickening of the subendothelial layer (Figs. 4 and 5). The endothelium at the site degenerated and a thrombus formed in

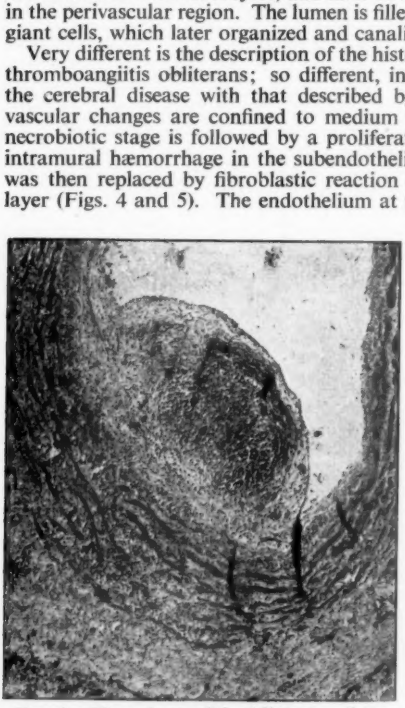

FIG. 4.—Thrombo-angiitis obliterans. Low magnification.

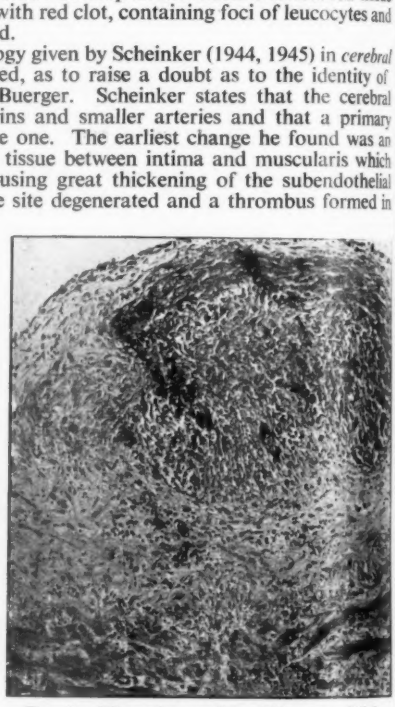

FIG. 5.—Thrombo-angiitis obliterans. High magnification.

the lumen which was converted into connective tissue canalized by vessels of relatively large size.

No lesions other than these intimal changes were observed in the vessel walls. The elastic membrane was usually preserved and the muscular layer was usually intact.

He states that no *inflammatory* changes are seen within or about the vessels, and suggests that the early intramural hæmorrhage is associated with reversible angiospastic and vaso-paralytic phenomena of prolonged duration and repeated occurrence. The adventitial and perivascular fibrosis seen in the periphery is not seen in the cerebral arteries.

Cerebral lesions.—The subarachnoid space is enlarged and the leptomeninges diffusely thickened. The lesions are mainly in the cortex and subcortical white matter. The affected gyri are yellow and shrunken and surrounding unaffected gyri show increase of cortical vessels.

Scheinker found in the brain several types of lesion: large or small areas of softening in the cortex or deep structures, cortical areas of granular atrophy, areas of tissue rarefaction

without gliosis, and small glial scars, all lesions presumably due to varying degrees and rates of production of ischæmia. Rarely softening has been reported in the brain-stem and cerebellum.

In the eye retinal and vitreous hæmorrhages, thromboses of the retinal artery, retinitis proliferans, and thromboses of the retinal veins have been reported in cases finally diagnosed as thrombo-angiitis obliterans of the retinal vessels. It is of interest that some of these occurred in cases diagnosed earlier as atypical multiple sclerosis, as tuberculous arteritis of the brain and as ophthalmo-encephalomyelitis.

Pathogenesis.—The disease has been attributed by Scheinker to recurrent prolonged periods of arteriospasm. He denies that there is any evidence of inflammation in the affected vessels and regards the lesions as necrobiotic.

There is a lot of evidence that arteriospasm occurs. When the disease affects the legs intermittent coldness, blanching and blue-mottling of the skin are seen in the early stages, and pulsation in the posterior tibial artery may be at one time present, at another absent. Similar attacks of blanching or transient cyanosis occur in the hands. Recurrent spasm was seen by Forster and Guttmann in one of the retinal arteries in a case of cerebral thrombo-angiitis obliterans not confirmed histologically. This spasm did not recur after homolateral resection of the superior cervical sympathetic ganglion and periarterial sympathectomy of the common and internal carotid arteries on the same side. In the cerebral vascular form the transience of early symptoms is compatible with the view that transient reduction occurs in the volume of the circulation to the areas of the brain involved, and this might be due to arteriospasm, though it could be explained if small arteries were permanently blocked and collateral circulation took up the blood supply to the temporarily infarcted area.

It is, however, common knowledge that spasm may follow upon arterial obstruction, a consequence rather than a cause. For example, arteriospasm throughout the lower limb follows popliteal embolism.

Thrombosis and embolism occurring in cerebral arteries have been seen experimentally to give rise to spasm in other parts of the same artery and in other cerebral arteries and veins. Such spasm may continue intermittently for months after the original obstruction.

Thus, arteriospasm of retinal or cerebral vessels might be expected to occur not only when cerebral vessels were blocked but also when proximal vessels such as the internal carotid artery itself was obstructed, and this might account for the clinical resemblance between many cases of thrombosis of the internal carotid artery and cases of thrombo-angiitis obliterans.

If, therefore, we accept as a fact that arteriospasm occurs in cerebral arteries in Buerger's disease of the brain two hypotheses to account for this are possible:

(1) That the spasm is the result and not the cause of Buerger's disease of cerebral arteries.

(2) That the spasm is the result of obstruction to the internal carotid artery which is itself the seat of Buerger's disease or some other thrombosing lesion. It is a fact that in some cases of recorded Buerger's disease of cerebral vessels the internal carotid artery has been found to be thrombosed at its origin.

In either case it remains unproven that the spasm leads to the changes characteristic of thrombo-angiitis obliterans in the spastic vessel. Lewis states that in severe cases of Raynaud's disease in the hands, digital arteries do eventually become thrombosed, but he does not describe the histological appearance of these arteries and thus it is not established that they are identical with those seen in Buerger's disease.

Prognosis.—Prognosis lacks a secure foundation until diagnosis in the early stages can be reasonably certain. This has not been the case with cerebral thrombo-angiitis obliterans, indeed, in most of the recorded cases diagnosis has only been made post mortem, or at operation.

Davis and Perret's 11 cases were diagnosed by direct inspection at operation for suspected cerebral tumour and on biopsy of vessels then removed. Among these cases there were 4 deaths and longer observation might have increased this number, but they are definite in their belief that recovery occurs.

The duration of recorded cases from the first appearance of cerebral symptoms is from eleven days to fifteen years, but many of the early years in the chronic cases are taken up by the slighter non-specific neurasthenic symptoms and it is probable that from the time definite symptoms of organic colour begin the duration of the disease to death does not much exceed five years and is usually much less.

Treatment.—There is no method of treatment known to have any certain beneficial effect on the course of the disease. Resection of both cervical sympathetic chains and periarterial sympathectomy were advised by Foerster, and 4 of his cases were said to have been thus improved though there is evidence that this measure does not cure the disease. If vasospasm

plays a part in the ætiology, the measure is a rational one. Intravenous injections of saline have been used. Vasodilators and anti-coagulants are without benefit (Davis and Perret).

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Dr. Henry Miller: *Clinical consideration of cerebrovascular disorders occurring during the course of general diseases of an inflammatory or allergic nature.*—Despite the suspicion with which allergy is regarded in neurological circles—suspicion justifiably based on the facile attribution of practically any mysterious or ill-understood syndrome to allergic causes—there can be little doubt that hypersensitivity reactions play an important part in a considerable field of human pathology. Experimental evidence has shown that the collagen-containing media of the smaller arteries is the main "shock-organ" of anaphylactic hypersensitivity, and experimentally and clinically it is clear that the cerebral vasculature may share to the full in this pathological process.

I shall consider first: Cerebral syndromes of vascular origin occurring in conditions where hypersensitivity plays a major pathogenetic role; and secondly, I shall review the evidence in favour of a relation of some similar mechanism to the cerebral vascular accidents of childhood and to the encephalomyelitic illnesses on the basis of which such accidents often arise. The final answers to the questions raised depend of course on more detailed and more numerous histopathological studies.

Serum sickness (Kraus and Chaney, 1937).—The reaction which follows repeated injections, or sometimes a single massive auto-sensitizing injection, of sterile foreign serum can be reproduced experimentally and represents the only one of these so-called collagen-vascular allergic diseases in which we can be certain of the exact ætiology. The histopathological basis of naturally occurring and experimental serum-sickness is the same, and consists in a disseminated focal infiltrative vasculitis in association with which is found focal œdema and whealing, and polyserositis. All the evidence suggests that the vasculitis is the essential lesion and the exudative reactions secondary to it. On the other hand the œdema itself as well as the arteritis—whealing of the brain as well as of the cerebral arteries—may well account for some of the rare but rather characteristic cerebral symptoms of the condition.

Many cases of serum sickness show spinal fluid changes even in the absence of neurological symptoms—raised pressure and protein, and a moderate lymphocytic pleocytosis. It is probable that the headache characteristic of severe cases is hydrocephalic. In some cases meningism or convulsions, and in others papillœdema or retrobulbar neuritis are seen. Polyneuritis and unilateral or bilateral cervical radiculitis are commoner than symptoms arising centrally, but amongst lesions which have been described in association with serum reactions are transverse or ascending myelitis, generalized encephalopathy giving rise to lethargy, stupor, and death in coma, and a variety of focal cerebral palsies. Monoplegia. hemiplegia, dysphasia, and hemianopia have all been described. Such symptoms have usually been transient, but occasionally are permanent, the former due to focal œdema, the latter either to actual hæmorrhage through a breach in the wall of a more severely damaged vessel, or to occlusion of an artery involved by panarteritis and obstructed either by mural œdema or thrombosis. Such changes in the intracranial arteries in human serum sickness have been demonstrated by Arnold Rich (1947). It is significant that although these cerebral syndromes usually occur in association with the exudative skin and joint manifestations of classical serum sickness, they sometimes follow foreign serum injection as isolated phenomena uncomplicated by urticarial or arthralgic features.

In parenthesis I would point out that the very rare neurological complications of *severe angioneurotic œdema* or *giant urticaria* are identical in quality and behaviour with those of serum sickness although they are usually less severe in degree (Kennedy, 1926). Amongst such complications described are headache, meningism, convulsions, papillœdema and retrobulbar neuritis, cranial nerve palsies, and focal cerebral palsies usually but not invariably partial in degree and transient in duration.

A more chronic and much commoner disease in which the symptomatology of allergic vasculitis is displayed is *polyarteritis nodosa*. There is no need for me to recapitulate the evidence of Rich and Gregory (1943) as to the non-specific allergic nature of the necrotic panarteritis of this disease and its histopathological identity with human and experimental serum sickness.

The characteristic neurological picture of polyarteritis nodosa is of course a painful

and often asymmetrical polyneuritis, due to obliterative arteritis of the vasa nervorum, and this is found in the majority of cases of the disease. Clinically, involvement of the central nervous system is considerably more rare. The usual figure given is about 20%, but transient cerebral symptoms certainly occur in a higher proportion of cases. Pathologically the most striking feature of the disease is its focal distribution along the course and around the walls of affected vessels. The attribution of symmetrical peripheral neuritis in the disease to general toxic rather than to local ischæmic causes arose because of the failure to examine serial sections of tissue, the nerve at many levels showing merely non-specific degeneration with intact blood vessels. That the same holds in the brain is certain, many sections revealing foci of degenerative change such as softening or gliosis but not the characteristic arterial lesions which caused them. Parker and Kernohan (1949), for example, found changes in the intracranial arteries in 70% of their recent cases, whereas the routine brain blocks of 15 cases of polyarteritis nodosa autopsied at Newcastle during the past few years yielded only one unequivocal instance of involvement of cerebral arteries even though several cases had shown cerebral signs including massive vascular accidents. As elsewhere in this disease the changes are those of patchy ischæmia sometimes with infarction or hæmorrhage. The changes may be disproportionately marked in one part of the brain, they may involve chiefly the carotid or the vertebral arterial systems, or they may spare the brain itself entirely, and affect only the meningeal vasculature. In addition to the changes in the wall of the vessel there may be perivascular infiltration. This again is patchy and usually not conspicuous. It may consist chiefly in microglial proliferation or in polymorphonuclear or lymphocytic infiltrations accompanied by perivascular softening or gliosis. The nature and degree of these perivascular changes are probably a function of the duration and chronicity of the disease. It should be noted incidentally that veins are often also to some extent implicated by this infiltrative vasculitis, and that in the acutest phases there is evidence also of damage to capillary walls with exudation and actual purpuric hæmorrhages.

Clinically it is not difficult to envisage the multiplicity of syndromes which have been encountered as a result of the capricious distribution of these lesions in the nervous system. Since the duration of polyarteritis nodosa may vary from a few days to as many years, the neurological symptomatology shows a similar variation between the acute picture seen in serum sickness and the syndromes of patchy infarction which we regard as typical of degenerative arteriosclerosis. Occasionally, in fact, the nature of the disease first becomes evident when a cerebrovascular accident ensues in the course of a featureless toxic illness characterized perhaps by fever, muscle pains, and peripheral neuritis. The commonest symptom of cerebral involvement is convulsions, and a local onset of the fit in a third of such cases indicates an origin in focal vascular changes rather than in the hypertension which is common in cases with marked renal involvement. Meningism is common, particularly in children; while confusional and dementing states (sometimes leading through stupor to death in coma), subarachnoid bleeding, pupillary changes, retinitis, papillœdema, and cranial nerve involvement may all occur. Focal cerebral symptoms such as hemiparesis are often irreversible. Cerebellar, extrapyramidal, brain-stem, and bulbar syndromes have all been encountered, and although spinal cord and cauda equina involvement is rarer I have seen several such cases. It is not surprising that erroneous diagnoses of multiple cerebral abscess, glioma, encephalitis, and atheromatous softening are sometimes disproved only at autopsy.

There are of course other diseases in which allergic vasculitis may well play a part, such as acute rheumatism and acute glomerulonephritis.

The acute cerebrovascular accidents of infancy and childhood.—The clinical and pathological similarity of the encephalomyelitic illnesses which occasionally follow vaccinia, measles, pertussis, scarlet fever, mumps, and a variety of other recognized and unidentifiable acute febrile diseases is striking. It was this very similarity which cast grave doubt on the original view that such complications were due to the acquisition of neurotropic properties by the causal viruses of the various initial illnesses, and led Dr. Greenfield in 1929 to suggest that they might be due to some unrecognized latent virus, activated by the original infection.

A very striking feature in the natural history of such cases is the regularity of their time-relationship to the preceding illness. Measles encephalomyelitis, for example, nearly always begins between the fourth and sixth days of the exanthem, post-vaccinal encephalomyelitis ten to eleven days after vaccination.

Clinically there is usually fever, drowsiness, headache, and meningism; while in severer cases there may be papillœdema, retrobulbar neuritis, and cranial nerve palsies leading particularly to ophthalmoplegias. A coincident generalized peripheral neuritis or a local meningo-radiculitis is not very uncommon. Convulsions, confusional states, cerebellar ataxia, paraplegia due to acute transverse or progressively extending myelitis, are all familiar in the severe cases, and these are of course not infrequently characterized by focal cerebral accidents leading to hemiparesis, dysphasia, or hemianopia. Rapid and complete recovery

may follow even the most profound disability. In some instances, however, and particularly when there is gross hemispheral damage, the residual disability is severe.

The following are 2 cases recently seen at the City Hospital for Infectious Diseases, Newcastle upon Tyne, the records of which were made available to me through the kindness of Dr. George Brewis. Both these cases of post-exanthematous encephalomyelitis, the one leading to permanent hemiparesis and intellectual deficit, the other fulminating and fatal, were associated with evidence of a vascular reaction of allergic type outside the nervous system:

The first was a boy of 6 who eight days before admission developed a febrile illness, the nature of which was not absolutely certain but which was probably mumps. On the seventh day of the illness he began to vomit, and this was rapidly followed by generalized muscular twitching, apparent blindness, and dysphasia. On admission he was unconscious, with neck stiffness and incontinence. During the ensuing days he developed an acute glomerulonephritis without much hypertension, enlargement of the liver with slight jaundice, and skin petechiæ. At various times he had internal and external ophthalmoplegias, gross bilateral tremor of the arms, and signs of pyramidal tract damage transiently on the left and more markedly and consistently on the right. There was a transient lymphocytic pleocytosis in an otherwise normal spinal fluid. Gradually his slight fever settled and he was left with a right hemiparesis accompanied by dysphasia and a profound intellectual deficit.

In this case then a fairly typical encephalomyelitis occurred in association with evidence of coincident vascular damage at least in kidneys and skin.

The second was a child of 5 with Fallot's tetralogy, discharged from the Middlesex Hospital on 29.1.50 because of chickenpox in the ward. On 12.2.50 she developed typical chickenpox and on 18.2.50 a further rash diagnosed as measles. Three days later she developed widespread urticaria, which over the course of the next seventy-two hours became purpuric. The child complained of headache, vomited, and became unconscious. Lumbar puncture revealed a bloody fluid but this, like blood culture, was sterile. Autopsy revealed generalized purpura with multiple visceral and cerebral hæmorrhages and active rheumatic carditis.

This encephalomyelitic picture arose then on the basis of purpura of anaphylactic type associated with acute rheumatic infection. If we accept the work of Gairdner (1948) such cases of purpura represent the most acute and catastrophic degree of allergic vasculitis, in which the brunt of the damage is born by the capillaries.

What then in summary is the clinical evidence for the close biological relation which I have suggested exists between cerebral serum sickness with its basis in allergic vasculitis, and post-infective encephalomyelitis?

The first suggestive feature is the constant time-relationship of the neurological complication to the initiating illness, which is so reminiscent of the relation with which we are familiar in acute glomerulonephritis and acute rheumatism. Secondly there is the striking similarity of the clinical manifestations in the two conditions (*see* Table I).

TABLE I

	Cerebral serum sickness	Poly-arteritis nodosa	Post-infective encephalo-myelitis
C.S.F.			
Raised pressure	+	+	+
Raised protein	+	+	+
Lymphocytosis	+	+	+
Headache	+	+	+
Meningism	+	+	+
Convulsions	+	+	+
Polyneuritis	+	+	+
Mononeuritis	+	+	+
Meningo-radiculitis ..	+	+	+
Papillœdema	+	+	+
Retrobulbar neuritis ..	+	+	+
Cranial nerve palsies ..	+	+	+
Transverse or progressive myelitis	+	+	+
Focal cerebral palsies ..	+	+	+
Brain-stem lesions ..	?	+	+
Cerebellar syndrome ..	?	+	+

There is surely no known virus infection which produces such a polymorphic picture of capricious involvement at every level of the nervous system from peripheral nerve to cerebral cortex. Again some of the symptoms—at any rate the more permanent focal cerebral palsies

—can hardly be other than vascular in origin. The only condition with which I am familiar in which such a picture is found is neurosyphilis and it is suggestive that here also the basis is an arteritis. Cases of encephalomyelitis associated with evidence of allergic vascular damage outside the nervous system provide further suggestive evidence in the same direction —that post-infective encephalomyelitis is in fact primarily a disorder of blood vessels and has its origin in a local incidence of allergic vasculitis.

There is of course nothing new in the attribution of post-infective encephalomyelitis to allergic causes (van Bogaert, 1933). We have recently, however, learned more about the histopathological basis of hypersensitivity and Rich has demonstrated its vascular basis. This new knowledge clarifies the mechanism by which both the encephalomyelitis and the associated vascular accidents may depend on a localized vasculitis as a manifestation of hypersensitivity.

A final decision on the question at issue depends on histopathological evidence which is at present lacking. Such evidence as is available does not at any rate render a close relationship between the two conditions an untenable hypothesis, even if for the moment we ignore the contributions of Ferraro and others in the experimental production of allergic encephalomyelitis. Considering the difficulty of demonstrating arterial changes in the brain in fully developed cases of polyarteritis nodosa with cerebral symptoms, the fact that so many authors have described infiltrative vasculitis as part of the pathological picture of encephalomyelitis is surely suggestive. Barlow, Creutzfeld, Bergenfeldt, Alpers, Grinker and Stone, Wohlwill, Ford and Hassin have all noted such a finding, and differentiation of some of their illustrations from the picture of cerebral polyarteritis nodosa is at least difficult.

The view which I have put forward would regard post-exanthematous encephalomyelitis as a manifestation of hypersensitivity to some antigen or antigens produced in the course of a variety of infections chiefly of a virus nature, and more or less localized to the cerebral vasculature; just as we believe acute glomerulonephritis is a manifestation of hypersensitivity to some antigen produced in the course of infection, usually though not invariably by the streptococcus, and chiefly though probably not solely involving the kidney. Experimental observations provide suggestive evidence that a selective local incidence of such manifestations of hypersensitivity may in considerable part be a function of the nature of the antigen.

If this view is correct it is possible that cortisone or ACTH may have more to offer therapeutically in an acute reaction of this nature than in the more chronic forms of vascular allergy, where the therapeutic response has all too often proved transient.

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Dr. **J. G. Greenfield** described a case of *giant-celled arteritis* which, although quite typical, amplified the clinical and pathological picture of this disease in some respects.

Mrs. E. H., aged 70, was admitted to the National Hospital, Queen Square, under the care of Dr. Grainger Stewart on 29.8.38 and died there a fortnight later. Her story was that she had been well till November 1937, when she began to have pain and stiffness in her hips, knees and shoulders and was treated for this through the winter at King Edward Memorial Hospital, Ealing. Her weight fell between Christmas 1937 and August 1938 from 13 to 9 st.

Early in July 1938 she began to have headaches with exquisite tenderness of the scalp so that it was very painful to brush her hair. Soon after this her eyesight began to be affected. At first her eyes ached and her vision became dim after she read for a short time, but after a week in this state her vision failed rapidly over a period of a few hours and she became blind. She was again admitted to King Edward Memorial Hospital on 6.8.38. At that time the left pupil was small, irregular and reacted to light. The right was large, irregular, and did

not react. There was slight bilateral papillœdema. The visiting ophthalmologist considered that the changes in the discs were not sufficient to account for her complete blindness. She was also complaining of soreness at the back of the head, and there was a diffuse, warm, tender swelling in the left occipital region. About a week after admission to the King Edward Memorial Hospital ptosis of the left eyelid became apparent, and the pupils ceased to react altogether. As the examination of the eyes suggested retrobulbar neuritis, she was transferred for further examination to the National Hospital, Queen Square. Examination there showed a widespread but patchy tenderness on touching the scalp on either side. She could not perceive light with the right eye, but with the left she got a faint impression of pinkness, when the light of an ophthalmoscope was shone into the eye. Both discs were pathologically pale especially in their temporal two-thirds. Nasally, especially in the right eye, the entering vessels passed over a raised mound of what appeared to be pale disc, before reaching its centre. They were, however, not hidden by swelling of the discs. The edges of the discs were fairly sharp and the discs appeared flat in their temporal parts. The pupils were unequal, the right being larger than the left. Both were irregular in outline, larger than normal, and completely fixed to light. There was slight, but definite ptosis of the left eyelid. No other abnormality was found on neurological examination. The blood pressure was found to be 110/50, and there was no undue thickening of the brachial vessels. Examination of the blood and cerebrospinal fluid showed no abnormality.

On 11.9.38, thirteen days after admission to the National Hospital, she complained of a sudden pain in the chest, sweated profusely, became collapsed and died in an hour. A post-mortem examination was made on the following day. Apart from some congestion of the small vessels toward the centres of the optic nerves just behind the optic foramina no abnormality was seen on naked-eye examination of the brain and spinal cord. The posterior halves of both eyes were removed after preliminary injection of formalin into the vitreous. In the heart, the anterior coronary artery was thickened with a very small lumen, which, however, appeared to be patent throughout. There was some congestion along the edges of this artery but no hæmorrhagic infarction of the heart muscle was seen. The aorta was atheromatous at its lower end but only slightly so elsewhere.

Histologically the lesions of giant-celled arteritis were found in the *anterior coronary artery*, the *internal carotid*, the *middle and anterior cerebral* and *anterior choroidal arteries*, and the *retinal* and *ciliary arteries* of both eyes.

The *anterior coronary artery* was sectioned just below its bifurcation on the anterior wall of the heart. In both branches the walls were greatly thickened, all coats being involved, but in diminishing degree from without inwards, with lymphocytic infiltration in all three coats and focal replacement of the media by epithelioid cells which had formed multinucleated giant cells.

In the *internal carotid arteries* there was little thickening of the wall of the vessel. Broad pads of atheromatous thickening of the inner coat were seen blending with, or more loosely attached to, the intima; lymphocytic infiltration here was slight. The media had for the most part disappeared. In some places it was very thin and in other places replaced by granulomatous thickening containing multinucleated giant cells. Deposits of calcium were seen between the media and intima. The adventitia was loose textured and heavily infiltrated with lymphocytes.

On both *middle cerebral arteries* in the fissure of Sylvius several small rounded or lentiform granulomas, one of which contained a central giant cell, and numerous small foci of lymphocytic infiltrations, were present in the adventitia. The media and intima showed no infiltrations and were healthy except where the media was thinned out or had disappeared, and there was compensatory thickening of the intima and adventitia. These might be healed lesions of arteritis but more probably were senile degenerative changes. The *anterior cerebral arteries* showed similar but slighter and apparently earlier adventitial granulomas without giant cells. In the left *anterior choroidal artery*, where it joined the choroid plexus, an area of granulomatous infiltration involving the media to some extent was seen on one side of the vessel wall. No tubercle bacilli could be found in any of these lesions. The *retinal and ciliary arteries* of both eyes were the seat of intense giant-celled arteritis which involved all three coats and reduced the lumen to a very narrow channel. In some places the media was entirely replaced by giant-celled granulomatous tissue; in others it was still recognizable. The thickening of the intima also varied but in most places was considerable. Lymphocytic infiltration was present in all three coats, but most intensely in the adventitia. Similar lesions could be traced into many of the scleral arteries for some distance away from the disc. The retinal arteries after gaining their position in the centre of the optic nerves showed no destructive lesions or thickening of their walls, but there was still considerable lymphocytic infiltration round them right up to the surface of the discs.

The *optic discs* in both eyes were hollowed out, with steep, almost vertical sides (Fig. 1), and were considerably sunken below the level of the sclera on either side. The appearances were those of glaucoma, rather than of optic atrophy of less than six weeks' duration. The only abnormality seen in the retinæ was sparseness of ganglion cells and shrinkage of those that remained. The inner and outer nuclear layers, the rods and cones, and the pigmented epithelium appeared quite normal. Both optic nerves showed early sudanophilic degeneration of myelin sheaths with a slight microglial reaction. No other lesions were found in the central nervous system. The temporal arteries were not examined.

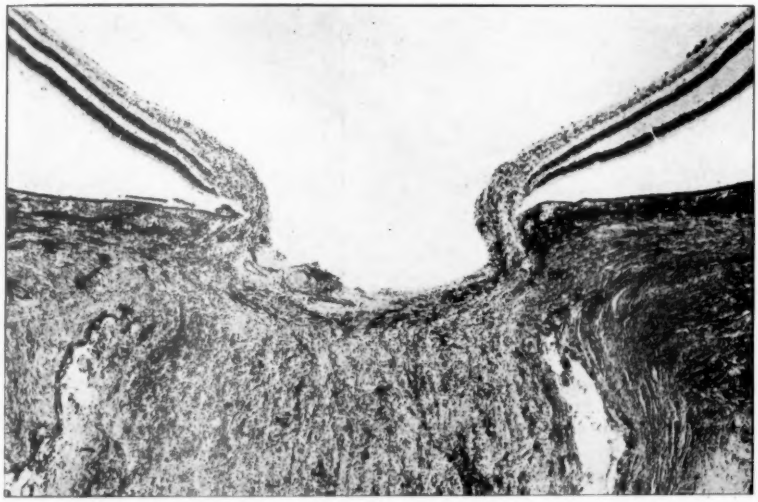

FIG. 1.—Section of optic disc and neighbouring retina to show the extreme hollowing of the disc. There is an area of lymphocytic infiltration at the side of the central artery. × 21.

It is unfortunate that no examination was made of the iris or ciliary body, or of the vessels in the anterior half of the sclera. Although no suspicion of glaucoma was entertained during life, the irregularity and fixity of the pupils taken along with the hollowing out of the discs suggest that glaucoma may have combined with partial ischæmia of the optic nerves and retinæ to produce blindness. This theory is supported by Andersen's first case (1947) in which bilateral glaucoma came on during an attack of temporal arteritis. Andersen attributed this condition, which remained subacute under treatment, to inflammation of the ciliary veins, but in the present case no lesion except mild lymphocytic infiltration of the adventitia was seen in these. The incomplete examination of the eye therefore leaves the pathogenesis of glaucoma in this case undecided.

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Mr. Wylie McKissock: It is to Olivecrona and Norlen of Stockholm that we owe the recent knowledge that a fair proportion of the intracranial angiomata can be excised with good results.

In my series of some 60 verified angiomata it has proved possible to perform a total removal in 19 cases with but a single death from an unsuspected atypical post-operative clot.

An important aspect of these vascular abnormalities is that the size of the lesion is no indication of the potential danger to the patient.

H. B-S., a woman of 36, had suffered a severe subarachnoid hæmorrhage and an attack of status epilepticus in each of which illnesses she nearly died. Arteriography revealed an angioma lying on the right superior frontal convolution just lateral to the mid-line (Fig. 1). Surgical excision was a simple matter, left no sequelæ and removed permanently the risks of future disaster.

I have had some 5 or 6 similar cases of which E. P-B., a left-handed girl of 18, is an excellent example. Suffering from thyrotoxicosis she developed in the course of a few days an aphasia, left hemianopia, hemianæsthesia and hemiparesis followed by a developing papilloedema. The possibilities of an intracranial abscess, hæmorrhage into a malignant tumour and a cerebral thrombophlebitis were considered. Biopsy of the right parietal region produced a few c.c. of altered blood which led to the performance of an arteriogram (Fig. 2). An angioma

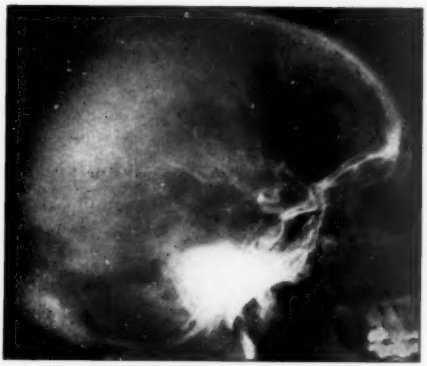


FIG. 1.—Lateral angiogram showing small right frontal angioma which had provoked one severe subarachnoid hæmorrhage and a subsequent attack of status epilepticus.

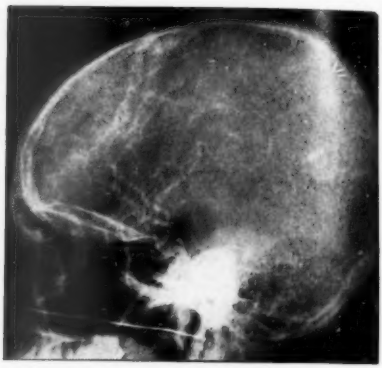


FIG. 2.—Lateral angiogram showing small right parietal angioma which had given rise to an enormous intracranial hæmorrhage simulating a rapidly expanding neoplasm.

1 cm. in diameter was revealed and at a subsequent operation was easily removed. An enormous intracranial clot was found deeply extending forwards for 10 cm. and deeply for 6 cm. Removal of angioma and clot was followed by disappearance of the signs of raised intracranial pressure, the patient being left with only a slight residual aphasia and a left lower quadrantic homonymous hemianopia.

It is evident, therefore, that even the smallest angiomata can threaten the existence of their host, surgical excision is often simple and risk of subsequent disaster is removed.

Dr. James W. D. Bull: There seems to be a large number of cases of subarachnoid hæmorrhage in which a cause for the bleeding cannot be found. Formerly it was supposed that a leaking aneurysm was nearly always responsible. During the last three years it has been the practice at the Atkinson Morley branch of St. George's Hospital to perform routine bilateral carotid angiograms on such cases (only one carotid artery is injected if a positive result is obtained). The following table shows the results:

Aneurysm	52 (62%)	Normal bilateral carotid angiograms ..	20 (24%)
Angioma	11 (13%)	? very small angioma	1 (1%)
		Total	84

One interesting feature is that in 13% angioma was the cause of hæmorrhage. In one case the angiograms showed some small vessels which I suspected of being angiomatous, but Mr. McKissock, under whose care the patient was, did not consider the evidence sufficiently convincing to justify exploration.

20 cases (24%) gave negative angiographic findings. Even if some of these cases had aneurysms of the vertebral arterial tree, the figure is, perhaps, too high to account for all of them since it is generally agreed that the great majority of aneurysms are found in the anterior part of the circle of Willis.

The cause of the hæmorrhage in some of these cases may have been a very small angioma—too small to be diagnosed by ordinary angiographic methods.

Section of Odontology

President—Sir WILLIAM KELSEY FRY, C.B.E., M.C., M.D.S.Durh., F.D.S., M.R.C.S.

[*March* 19, 1951]

The Architectural Pattern of the Boundary between Epithelium and Connective Tissue of the Gingiva

By R. D. EMSLIE, B.D.S., F.D.S., M.S. (Illinois)
(*Dental Department, Guy's Hospital, London*)

Introduction.—The morphology of the boundary between epithelium and connective tissue of the gingiva has been extensively studied in histological sections. However, such two-dimensional pictures of the complex patterns of these tissues are sometimes difficult to interpret, and it was felt that a three-dimensional study of this region would clarify the histological picture. It has also been stated that an early sign of pathology in gingivitis is a proliferation of epithelial papillæ into the lamina propria. In this paper an attempt has been made to demonstrate the normal pattern of the epithelio-connective boundary or junction, and the changes which occur with inflammation.

Material.—Part of this study was upon the gingiva of the Rhesus Macaque monkey, and was undertaken at the University of Illinois. These findings have been published in the *Anatomical Record* (Emslie and Weinmann, 1949). Sixty biopsy specimens were taken from 12 living Rhesus monkeys under nembutal anæsthesia, and the jaws of two monkeys were sectioned and examined histologically. The ages of these animals ranged from 18 months to 5 years.

The animals were maintained on a diet of fresh lettuce, apples, bananas and carrots, augmented by bread and milk. Their gingival condition was generally excellent, although some showed slight inflammation of the interdental papillæ in the upper incisor region.

The remainder of the study was made at Guy's Hospital upon human material removed by gingivectomy. Specimens were taken from 20 patients whose ages ranged from 12 to 57 years. 5 of the patients were taking dilantin sodium for the control of epilepsy.

Methods.—The various separation techniques reviewed by Emslie and Weinmann (1949) were tested, and the old acetic acid maceration method was found to be the most effectve for complete and easy separation of gingival biopsy specimens. A strength of 0·25% or 0·5% acetic acid was used, and immersion for periods of six to forty-eight hours, dependent upon the size of the specimen, permitted the epithelium to be peeled off with tweezers.

After separation the specimens were kept in 5% formalin. They were examined with a dissecting microscope and photographed in glycerin or water using a low magnification and oblique illumination.

Observations.—A. Rhesus Monkey Material:—

(1) The loosely attached alveolar mucosa (Orban, 1948) showed the simplest pattern of the boundary between epithelium and connective tissue. The epithelium was a flat sheet, pitted at intervals by short, conical connective tissue papillæ (Fig. 1).

(2) In the attached gingiva the connective tissue papillæ were larger in size and more numerous per unit area. This produced a "honeycomb" appearance in the epithelium, with more prominent vertical ridges (Figs. 2 and 3).

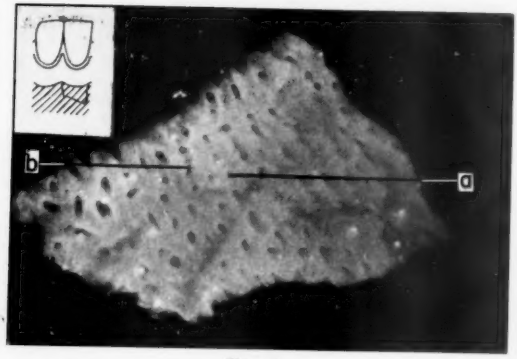
(3) In the free gingiva, the epithelial honeycomb was similar to that of the attached gingiva. At the gingival margin the horizontal ridges of the honeycomb were more prominent than the vertical ridges and ran parallel to the margin.

(4) The epithelial attachment of teeth in functional occlusion was pitted by connective tissue papillæ. The direction of these papillæ was almost parallel to the long axis of the tooth (Fig. 4).

(5) The palatal mucosa showed well-developed ridges in the epithelium and connective tissue, although these ridges were smaller and more closely arranged than in the attached gingiva. Pits in the troughs between the epithelial ridges were always present. They were produced by papillæ arising from the crest of the connective tissue ridges.

(6) In mild chronic inflammation the main ridges of the epithelium were thickened, but with a greater degree of inflammation a downgrowth of some of the epithelial ridges into the connective tissue had occurred (Fig. 5).

(7) Epithelial pegs or epithelial papillæ were rarely found in the gingiva.



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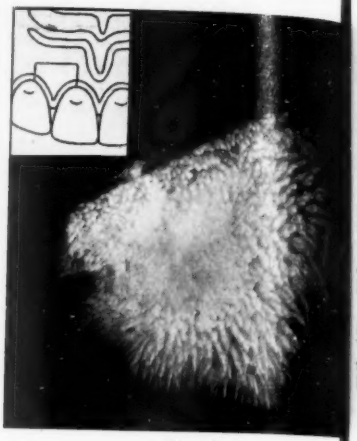

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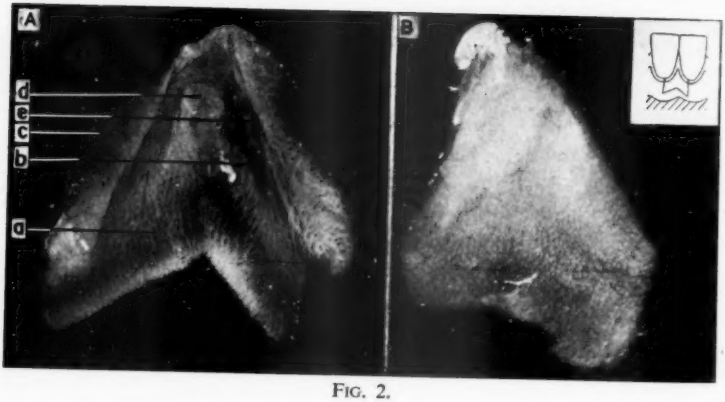

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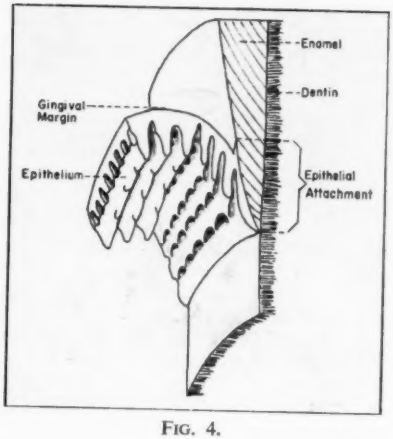

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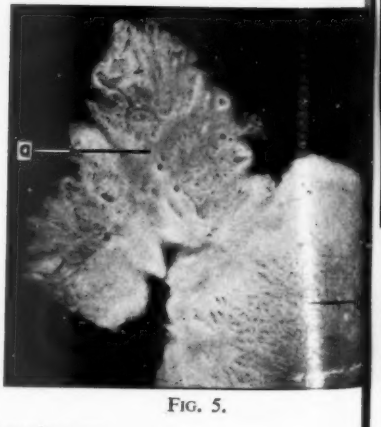

FIG. 5.

Legends FIGS. 1—5 *see* opposite page.

FIG. 1.—Photograph of the undersurface of separated epithelium from a biopsy of the alveolar mucosa of the lower central incisor region of a young adult monkey. The area of the biopsy is indicated by the insert. The epithelium appears as a flat sheet containing regularly arranged pits (a) which are connected by shallow grooves (b). × 40.

FIG. 2.—Photograph of the undersurface of the separated epithelium (A) and the surface of connective tissue (B) of an interdental papilla obtained in a gingival biopsy from a young adult monkey. The area of the biopsy between the lower central incisors is indicated in the insert. Note in (A) the epithelial honeycomb of the attached gingiva (a), the parallel ridges of the marginal area (b), the pits in the epithelial attachment (c), the epithelial whorl (d), the epithelial dome (e). × 16.

FIG. 3.—Photograph of the lamina propria of an interdental papilla from a biopsy of the palatal side of the upper incisor region of a young adult monkey. The area of biopsy is indicated in the insert. Note the large number of fine conical connective tissue papillæ. × 30.

FIG. 4.—A diagrammatic representation of the free gingiva and epithelial attachment after the connective tissue had been removed. Note pits in epithelial attachment running almost parallel to long axis of tooth, and pits in sulci between epithelial ridges at gingival margin.

FIG. 5.—Photograph of the undersurface of the epithelium from a gingival biopsy of a chronically inflamed interdental papilla from between the upper central incisors of a young adult monkey. The region of the tip of the papilla (a) shows a coarse honeycomb pattern, the large "cells" being subdivided into smaller pits at their blind ends. Further away from the source of the irritation, a honeycomb, which is normal except for thickened ridges (b), is seen. × 20.

FIG. 6.

B. Human Material:—A study of stained sections and separated tissues revealed no fundamental differences between the pattern of the epithelio-connective tissue boundary in the Rhesus monkey and man. Such differences as were found were associated with a much greater degree of inflammation in the human material, all of which was taken from cases of advanced periodontal disease.

Fig. 6 shows the undersurface of epithelium removed by gingivectomy from the upper incisor region of a male aged 25. The condition had been diagnosed as periodontitis simplex, and was associated with a lack of lip seal. A "thickened honeycomb" appearance in the epithelium of the attached and free gingiva was found, with some proliferation of the pocket epithelium.

A "double honeycomb" effect is seen in Fig. 7. This is a photograph of epithelium from the lower incisor region in a male aged 35, with periodontitis simplex. Some of the ridges of the fine honeycomb have proliferated, producing a coarse honeycomb of large "cells", with smaller pits at their blind ends.

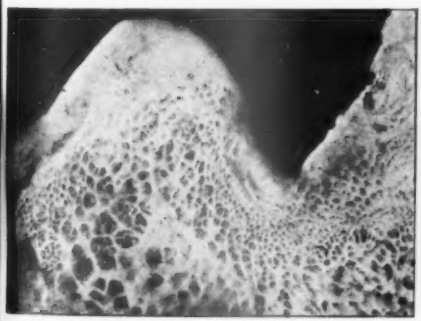

FIG. 7.

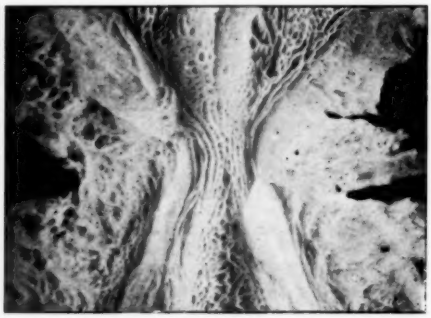

FIG. 8.

The undersurface of the epithelium of an interdental papilla between $\underline{1}|1$ from a female aged 29 is shown in Fig. 8. The X-ray appearance of the alveolar bone showed the "vertical" bone resorption typical of periodontitis complex. Proliferation of the pocket epithelium, and thickening of the ridges of the epithelium of the oral surface of gingiva, has occurred.

The typical appearance of the proliferation found in the gingival epithelium of the 5 patients taking dilantin sodium is shown in Fig. 9. This specimen is epithelium from the hyperplastic upper incisor region of a female, aged 17, who had been taking the drug for

some years. The change from the normal pattern is marked, with an irregular downgrowth and thickening of the epithelial ridges.

Several of the separated specimens were sectioned and stained with hæmatoxylin and eosin to check that the layer of separation was in the basement membrane between the epithelium and connective tissue. Fig. 10 shows such a specimen from the upper incisor region of another female aged 17 who was taking dilantin sodium. Depressions on the surface of the epithelium, partly filled with desquamated cells, may be noticed. These appear to form the stippling of the gum which is often marked in dilantin hyperplasia. These stipples occur where the deeper epithelial ridges of the honeycomb intersect.

A rather similar type of epithelial proliferation to the dilantin cases was found in a female aged 12 with an idiopathic gingival hyperplasia (Fig. 11). Several gingivectomies had been performed on this patient at various hospitals, but the condition had always recurred.

FIG. 9.

FIG. 10.

FIG. 11.

FIG. 9.—Note the irregular downgrowth and thickening of the epithelial ridges.

FIG. 10.—Note appearance of proliferated epithelium.

FIG. 11.—Epithelium from upper incisor region.

DISCUSSION.—Various changes which may occur in the architecture of the epithelio-connective tissue boundary have been demonstrated. It has been suggested that proliferation of processes of the gingival epithelium is an early sign of pathology in chronic gingivitis, occurring before any downgrowth of the epithelial attachment.

King (1944) on the basis of sections of decalcified ferret's jaws with varying degrees of gingival disease, stated: "The foregoing illustrations have demonstrated the displacement of the fibrous tissue and other components of the corium by proliferating epithelial papillæ." He believed these changes to be similar in many ways to those of certain types of gingival disease in man. In the same paper he described a "bushing" of the peripheral capillaries in the lamina propria, as seen with a capillary microscope in living and dead animals. The "bushing" was, in his view, a fairly early sign of gingival pathology.

In the present study it was found that in regions showing clinical signs of chronic inflammation in the gingiva of the Rhesus monkey and in man, the main epithelial proliferation occurred in some of the ridges which extended deeply into the lamina propria. The normal fine epithelial honeycomb was changed to an irregular pattern with much larger honeycomb cells containing the smaller normal cells as subsidiary pits.

Serial sections demonstrated that fine connective tissue papillæ in such pits had only one capillary loop running to the tip, but the wider papillæ contained more capillaries. Small blood vessels in large connective tissue papillæ, branching into a capillary loop for each peripheral papilla, would produce a "bushing" effect as described by King.

CONCLUSIONS.—(1) The epithelio-connective tissue junction is adapted to provide a greater blood supply in the masticating mucosa (i.e. free and attached gingiva and palatal mucosa) than in the alveolar mucosa. This increased nutritional demand is probably associated with a greater mitotic activity in the germinating layers to replace the cells desquamated at the

surface, and the biochemical changes of hornification. The increase in size and number of the connective tissue papillæ permits more capillary loops to approach the basal layer of epithelium.

(2) A better mechanical bond between the epithelium and connective tissue in these regions is provided by the well-marked ridges.

(3) Epithelial pegs are seldom found in the gingiva. Therefore, the use of such terms as epithelial pegs or papillæ should be abandoned, unless it has been determined that any particular epithelial process in question is actually of peg form.

(4) Once the tooth has erupted into functional occlusion, connective tissue papillæ are normally found in a part, at least, of the epithelial attachment.

(5) Such appearances as "blunting", "spiking", "rounding", or "clubbing" of epithelial processes in sections might be produced by sectioning the epithelial honeycomb at different angles (Fig. 12). Caution should be exercised before attaching any pathological importance to such findings when only one or two sections are available. Many sections should be examined before the term "acanthosis" can safely be applied.

(6) Various changes in the epithelial pattern occur with inflammation and hyperplasia of the gingivæ. Swelling of the ridges of the epithelial honeycomb may be the only change, or a proliferation of some of the ridges may develop, producing the double honeycomb effect. Gross hyperplasia of the gingiva which often occurs in patients taking dilantin sodium is associated with a marked irregular downgrowth of epithelial ridges.

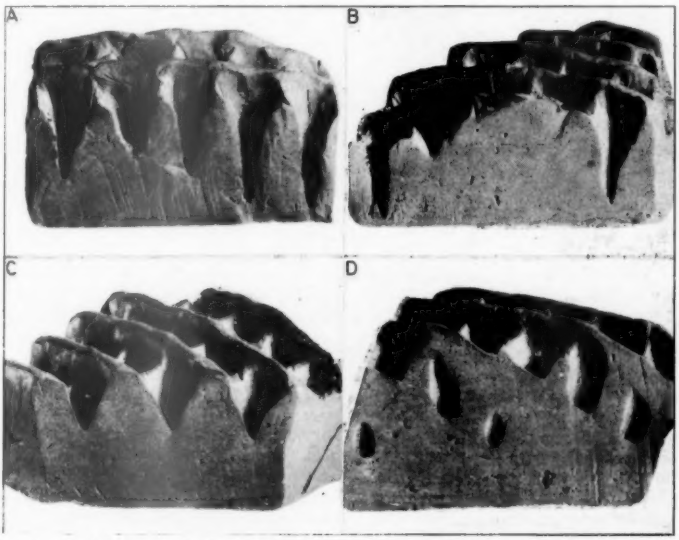

FIG. 12.—A plasticine model of an epithelial honeycomb similar to that found in the attached gingiva. This model has been sectioned in various planes and shows some of the different pictures which may be obtained. In (A) the line of section runs at right angles to the surface, parallel to the main epithelial ridges, and practically midway between two of them. B shows a similar section at right angles to the surface, but cutting obliquely through one of the main epithelial ridges. C shows a section at right angles to the surface, but cutting through the main epithelial ridges at 45 degrees. D shows a section at 45 degrees to the surface, also cutting obliquely through main epithelial ridges.

It is suggested that the most simple way of determining the architectural pattern of the epithelio-connective tissue junction in a biopsy of the gingiva is by a study of a few stained sections of the specimen together with a low power examination of the undersurface of the separated epithelium.

I should like to thank Dr. J. P. Weinmann of the University of Illinois for his help and encouragement, and Mrs. M. E. Small, Dental Photographic Department, Guy's Hospital, for the photographs of the human specimens.

Figs. 1–5 and 12 are reproduced by kind permission of the publishers of *Anatomical Record.*

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Mr. P. H. Staple congratulated the speaker on introducing a technique which dispensed with "the fatal facility of the microtome" and enabled tissues to be studied without introducing the artefacts consequent on embedding and section cutting. In particular, the results which Mr. Emslie had obtained on tissues from patients receiving dilantin sodium had been invaluable in the interpretation of sections of the same tissues which were being used to study the reactions of the underlying connective tissue.

Perhaps more important was the opportunity this type of technique offered to carry out biochemical investigations on gingival epithelium apart from connective tissue. Previous workers in this field had used whole tissue, i.e. epithelium and connective tissue; it would be of great interest to know whether changes in glycogen content occurred in epithelium or whether they were confined to the connective tissue. In some cases other methods available for tissue separation would have to be used, since acetic acid reacts with many tissue substances.

That acetic acid allowed the separation of epithelium from the ground substance of connective tissue but did not cause the epithelium to disintegrate suggested that the mucopolysaccharide of the epithelial intercellular cementing substance differs from that of ground substance. Alternatively, this disintegration may be prevented by the presence of intercellular bridges, usually described only in the "prickle-cell" layer, but which, in "frozen dried" material, are seen to extend almost up to the level where keratinization begins.

It was suggested that a basement membrane separated gingival epithelium from the underlying connective tissue. A study of "frozen dried" material indicates that this structure may be an artefact arising from fixation or techniques used subsequently.

[*April* 23, 1951]

Neurofibroma of the Mandible

By H. J. J. Blackwood, M.B., B.Ch., B.D.S., and R. B. Lucas, M.D., M.R.C.P.

Neurofibroma is an infrequent tumour in the oral region. When it does occur the tongue is the most usual site, a number of cases having been reported by Stout (1935), Willis (1948) and others. Goldman (1944) has recorded a neurofibroma of the maxillary sinus, and tumours of the palate have been described by Stout and by Christiansen and Bradley (1946).

The mandible is very rarely affected. Zilkens (1937) reported a case in which the tumour was situated in the incisor region of the mandible and Goldman (1944) described a neurofibroma extending from the premolar region to half-way up the ramus. In Rushton's (1944) case the tumour, though involving the mandible, apparently had its origin in the soft tissues of the cheek.

Case Report.—P. McI., male, aged 41.

History.—The patient had sought advice on account of a clicking sensation in his left ear, which he dated from a blow on the face some five months previously. A swelling in the $\lfloor\overline{56}$ region of the mandible was discovered, and he was referred to the Royal Dental Hospital under the care of Mr. C. Bowdler Henry.

On examination, there were no abnormal clinical findings in the mouth except for slight expansion of the buccal plate of bone in the $\lfloor\overline{56}$ region. The teeth reacted to vitality tests and no disturbances of sensation were elicited in the cheeks, lips or tongue. A general examination also proved negative.

X-ray examination (Figs. 1 and 2) revealed a large, radiolucent area beneath the apices of $\lfloor\overline{56}$, which appeared to be due to expansion of the inferior dental canal. There was slight resorption of the apex of $\lfloor\overline{5}$ and mesial apex of $\lfloor\overline{6}$. These two factors suggested the possibility of a solid tumour. X-rays of other bones revealed no abnormality.

Under endotracheal anæsthesia the buccal plate of bone was removed in the $\lfloor\overline{56}$ region exposing a tumour mass lying beneath the apices of $\lfloor\overline{56}$. These teeth were extracted and the tumour enucleated

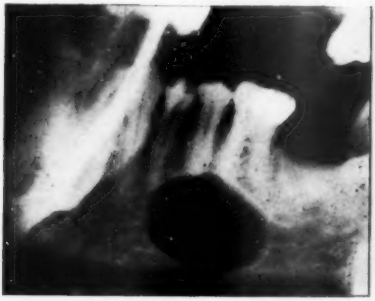

Fig. 1.

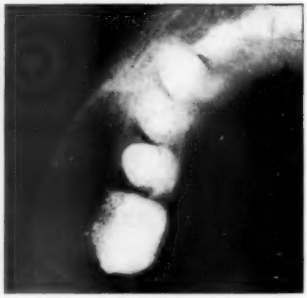

Fig. 2.

Fig. 1.—Showing expansion of the inferior dental canal and slight resorption of the apex of $\lfloor\overline{5}$ and mesial apex of $\lfloor\overline{6}$.

Fig. 2.—Occlusal view.

cleanly and easily. Some tags of tissue were left in the cavity, but these appeared to arise from the inferior dental canal. The wound was closed directly. Convalescence proved uneventful except for anæsthesia of the left lower lip.

Pathology.—The tumour was a well-circumscribed ovoid mass measuring 2 × 1·5 × 1 cm. The cut surface was of a translucent, greyish appearance, quite soft in consistency and showing small cystic areas and minute hæmorrhagic spots.

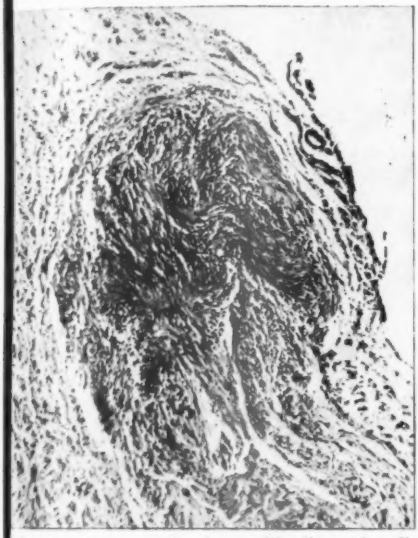

FIG. 3.—An area showing pallisading of cells surrounded by a zone of looser tissue. × 50.

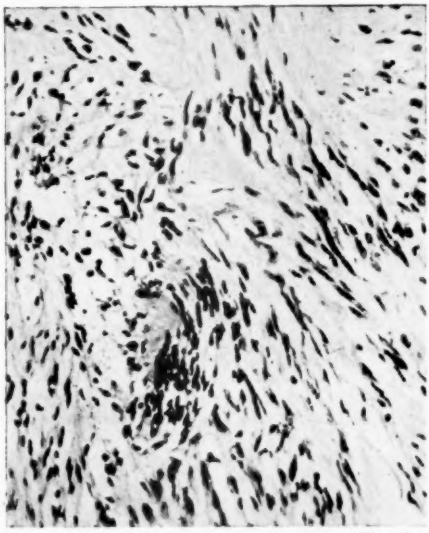

FIG. 4.—Detail from Fig. 3, showing pallisading and intercellular vacuolation. × 200.

Microscopically the two types of tissue characteristic of neurofibroma were found: Type A, which shows a parallel arrangement of cells and intercellular fibres giving a regimented appearance, and Type B, which consists of a loose meshwork of cells and shows the presence of numerous intercellular vacuoles or microcysts (Figs. 3 and 4).

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[*May* 28, 1951]

Actinomycosis of the Jaws in an Antelope (*Ourebia kenyæ*)

By A. E. W. MILES, F.D.S., M.R.C.S., L.R.C.P.

THE skull of a female oribis, presented to the Museum by the Zoological Society of London, is of interest because the jaws are affected by actinomycosis. The animal, a small African antelope (*Ourebia kenyæ*), lived in captivity for four years and died from pneumonia as a complication of the actinomycosis of the jaws.

The skull, of which the mandible is incomplete, is that of a young adult animal. In the region of the cheek teeth of both jaws the bone is much expanded with a very thin, fragile cortex, the central portion having been destroyed. The teeth are all present but have fallen out of the expanded bony cavities *post mortem* (Fig. 1). Attached to the roots of the affected molars are rounded masses of calcified tissue which exhibit a remarkably detailed symmetry between the two sides. A ground section through one of the smaller calcified masses, attached to the anterior root of the left mandibular M_3, shows it to be composed of cementum (Fig. 2). The centre is formed of an aggregation of several nodules of calcified tissue of very irregular structure, surrounded by a cortex of cementum of more regular lamellar structure.

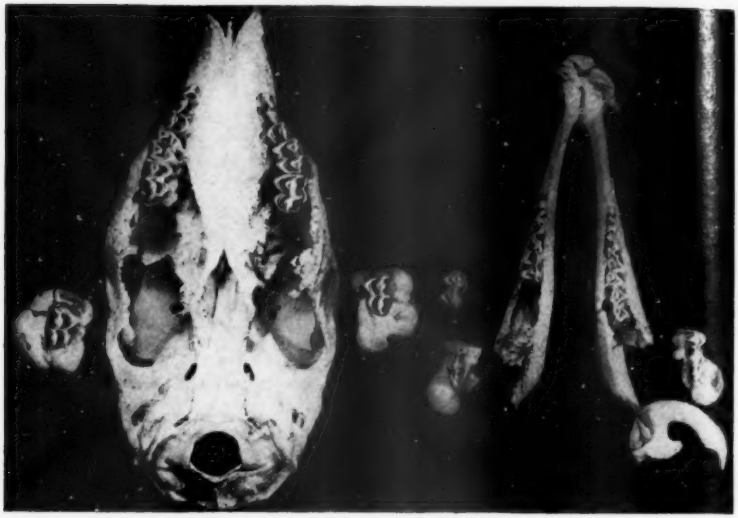

FIG. 1.—*Ourebia kenyæ*. Skull showing actinomycosis of maxilla and mandible with symmetrical hyperplasia of cementum of affected roots. (R.C.S. Museum, Odont. Sect. Cat. No. G 51.721.)

FIG. 2.—Ground section through apex of anterior root of left mandibular M_3 showing attached mass of cementum. × 6. a, dentine of root. b, apex of curved root. c, aggregation of nodules of calcified tissue of irregular structure. d, cellular cementum of regular structure.

In man actinomycosis affects the soft parts in relation to the jaws and rarely affects the bones (Cope, 1938), whereas in animals the bone is commonly affected. There is evidence that, as in man, the actinomycosis of cattle is in most cases due to infection with a strictly parasitic actinomyces which is a normal inhabitant of the mouth, although in a few cases the causative organism may be the aerobic soil fungus commonly found on grasses.

In animals the portal of entry appears frequently to be the teeth, very often through a parodontal lesion due to food packing between the teeth. This explains why the region of the cheek teeth is most commonly affected, as in the present specimen. According to Hutyra, Marek and Manninger (1946) the mandible is more commonly affected than the maxilla and there is a progressive destruction of the central cancellous bone with replacement by granulation tissue which may be found growing up around the teeth. At the same time there is a new formation of periosteal bone, resulting in expansion of the affected jaw. The present specimen, therefore, shows the changes that are characteristic of actinomycosis of bone. The hyperplasia of cementum has no doubt arisen as a result of the irritation of the low-grade actinomyces infection. The symmetry of the hyperplasia, however, is a curious feature which would appear to have a genetic basis.

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Section of Obstetrics and Gynæcology

President—V. B. GREEN-ARMYTAGE, F.R.C.O.G., M.D., F.R.C.P.

[*April* 20, 1951]

Some Structural Defects in the Upper Uterine Segment, Associated with Abnormal Uterine Action in Labour

By A. C. PALMER, F.R.C.S., F.R.C.O.G.

My purpose is to unfold certain ideas which have been taking shape during the last fifteen years.

There are two things to consider: First, the structural changes or defects in the upper segment; and second, the abnormal behaviour of the uterus associated with these changes and possibly caused by them. All the structural changes have been noticed in the course of performing Cæsarean section. In some instances, the operation has been performed because progress in labour has ceased, in the absence of mechanical obstruction, and in spite of what appeared to be competent uterine contractions. In other cases, the defects have been noticed at elective operations. The changes noticed arrange themselves into three groups which to some extent overlap. In all groups, a part of the muscle of the upper segment appears to be much thinner than the adjacent muscle. This appearance is present when the uterus is empty, contracted and retracted, but has been noticed in the first place, immediately after extracting the child.

GROUP 1: *Localized thin oval or circular areas in the fundus, without effect upon the course of labour.*—These areas are rarely bigger than a crown, they tend to cluster in the fundus and usually site themselves in one or both cornua just inside the tubal region. Occasionally, a single oval area may be in the middle of the fundus. Sometimes the areas in each cornu will be joined to each other by a thin strip across the fundus and give the appearance of a flat dumb-bell.

These areas have been found by chance in elective Cæsarean section performed for gross disproportion, toxæmia or placenta prævia, in women who had previously had a normal labour. They are believed to have no influence on the course of labour, unless the area is large enough to sacculate during pregnancy and allow the adjacent fœtal part to slip into the sac. As will be shown later, sacculation does occur during pregnancy and probably enlarges, at least in some cases, during labour.

Areas of this nature have been noticed in 14 cases and are shown in Fig. 1.

GROUP 2: *Changes associated with abnormal uterine action* (7 cases).—Three localized areas occurring as a sub-fundal girdle below the level of the tubes. Horseshoe-shaped strips of thin muscle, stretching over the fundus and down the upper segment, sometimes reaching the lower segment.

These thin horseshoe strips may be present without noticeable change in the rest of the muscle. Sometimes, the muscle on either side of the horseshoe will appear unduly thickened and form two thick muscular caps, which tend to be unequal in size.

Fig. 2 shows lateral caps of equal size.

Fig. 3 shows caps of unequal size, that in the right cornu being sacculated, and containing fœtal head.

GROUP 3: *Local or general sacculation of the posterior wall of the uterus* (2 cases of abnormal uterine action; 1 elective operation).—Here, the sac wall has been very thin, perhaps about one-quarter of the thickness of the anterior wall. These sacs differ from the horseshoe sacculation where the muscle has appeared normal or unduly thick. When they have contracted down to the level of the uterine wall, they occupy only a part of the posterior surface. I suspect the local sac has been formed during pregnancy because the head of a breech presentation has been lying in contact with a rather large thin oval or circular area in the posterior wall. Apparent sacculation of the whole of the posterior wall may be explained in a similar manner. It probably enlarges during labour. When the uterus retracts after delivery, the sacs slowly subside to the level of the uterine wall and their site is indicated by the peritoneal surface being wrinkled. The thickness of the sac wall is still only about a third of the thickness of the rest of the upper segment. One local sac contained the fœtal head while another contained the upper lobe of a bilobular placenta.

Fig. 4 shows fœtal head in localised posterior fundal sac, with thin wall.

Fig. 5 shows thin-walled sacculation of whole of posterior wall of upper segment.

An outstanding feature of these cases has been more frequent and more painful contractions than would be expected in the early stage of dilatation of the cervix, and they have been present for a much longer time than usual, with the result that the patient has become physically and emotionally fatigued—in some cases exhausted—before the external os is appreciably larger than half a crown.

Summary of type of labour.—The start, in all, has resembled primary uterine inertia, that is to say, feeble pains at half-hourly intervals for eight to ten hours.

The next stage is variable. Some cases pass straight away into strong painful frequent contractions and at the end of twenty-four hours there is no change in a cervix which admitted 1 or 2 fingers twelve to fourteen hours earlier. Now, the patient is getting tired and, in my view, this is the time to make a decision and terminate the labour by Cæsarean section. In other cases, the initial feeble pains subside and secondary uterine inertia may exist for twenty-four hours. This sequence may be repeated before the severe contractions make their appearance.

When the strong contractions start they soon become severe, then very severe at three to five minute intervals and, in spite of sedatives, continue without appreciable relief and without noticeable change in the cervix for two or three days.

I now believe that a patient who has been in this condition for twelve hours has had ample trial and that the labour should be terminated by Cæsarean section. If the labour is allowed to continue, the uterus eventually fails to relax completely between pains, it becomes difficult to control the patient and the need for operation is urgent.

For convenience and brevity, I am now using the term "First-stage Uterine Colic" to describe the strong frequent painful contractions without dilatation of the cervix. The onset of uterine colic appears to be accompanied by cessation of the expulsive action of the uterus and its replacement by a squeezing action.

It cannot be doubted that this type of labour is uncommon.

I believe that in some cases where the muscle defect is not gross and the child is small, the cervix may eventually dilate sufficiently, to allow delivery by the vagina.

Conclusion.—The association of structural defect with bad uterine behaviour is constant in this series and leads one to suspect the association to be that of cause and effect. It may be that imperfect structure interferes in some way with uterine innervation. At present, the arrangement of muscle fibres at the junction of thick and thin areas is not known, as there has been no opportunity of removing such a uterus at operation.

It is suggested that the defects may be the result of imperfect fusion between those parts of the Müllerian ducts which form the body of the uterus.

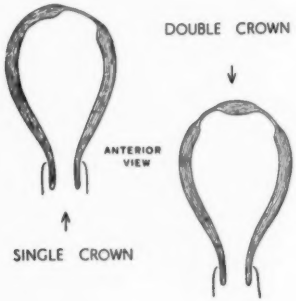

FIG. 1 (*Case A*).
Diagram showing the type of fundal defect seen in 14 cases and believed to have no influence on the course of labour.

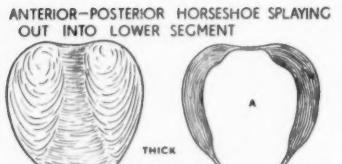

FIG. 2.

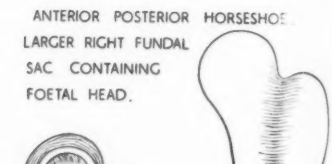

FIG. 3.

FIG. 2 (*Case B*).—*Antero-posterior horseshoe with thick fundal caps.* Aged 27. First pregnancy. Sixty-two hours in labour. Primary uterine inertia. Membranes ruptured after thirty-one hours, cervix 1 finger. Twenty-four hours later cervix unchanged after six hours of uterine colic. 8 oz. Champetier bag inserted with 2 lb. weight; expelled in five hours. Cervix closed down to 2 fingers. Uterine colic persisted and Cæsarean section performed.

Condition of uterus remained unchanged at second Cæsarean section, two years later.

FIG. 3 (*Case C*).—*Antero-posterior horseshoe with thick-walled sacculation in each cornu.* Aged 34. First pregnancy. Breech with extended legs, head beneath right lower ribs. Elective Cæsarean section became an emergency after onset of labour. Head delivered from fundal sac by jaw and shoulder traction. Primary inertia type.

Mr. G. F. Gibberd has suggested that the appearance of structural change may be due to physiological variation in uterine action. This suggestion offers an attractive explanation of thin-walled sac formation. The empty sac slowly shrinks to the level of the retracted uterine body, and its wall is now about one-third as thick as that of the adjacent muscle. In the process of involution the muscle of the upper segment may become uniform in depth. I have not yet examined such a uterus on completion of involution, and do not know whether this change takes place.

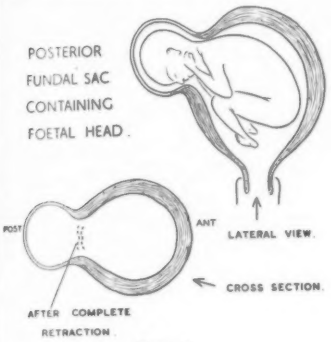

FIG. 4.

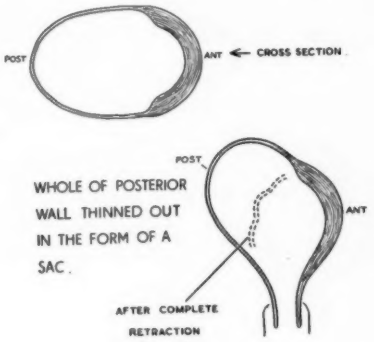

FIG. 5.

FIG. 4 (*Case D*).—*Posterior fundal thin-walled sac formation.* Age 36. Third pregnancy. Breech. 1st labour: prolonged; four days. 2nd labour: Cephalotripsy for disproportion. 3rd pregnancy: Elective Cæsarean section. Sac discovered at operation; delivery of head by jaw and shoulder traction from sac, which slowly contracted to level of wall of empty retracted uterus. Peritoneal surface of thin area wrinkled.

FIG. 5 (*Case E*).—*Thin-walled sac formation of whole of posterior wall.* Aged 22. Second pregnancy. 1st labour: twenty hours; forceps; child 5 lb. 9 oz. 2nd labour: forty-two hours; child 6 lb. 15 oz. Moderate toxæmia. Spontaneous rupture of membranes before onset. Primary inertia; secondary inertia; uterine colic fifteen and a half hours, cervix 2 fingers. Sacculation of posterior wall discovered at operation and seen to contract slowly after retraction of thick anterior wall. Peritoneal surface of sac wrinkled.

(Figs. 1–5 are drawn by T. R. Tarrant.)

Activity of the Cervix of the Human Uterus and its Response to Drugs

By H. O. SCHILD, M.D., Ph.D., D.Sc.

THERE has been some doubt in the past whether the human cervix can contract independently, but recent work by Woodbury (1944) and Karlson (1949) shows fairly clearly that the cervix can contract and that the contractions recorded from the cervix are true muscular contractions and not artefacts transmitted from the uterus. Very little is known of the action of drugs on the cervix of the human uterus, but some work has been done on the reaction of the cervix of various laboratory species both *in vitro* and *in vivo*. Newton's *in vitro* work (1934, 1937) suggested that the cervix, although capable of responding to adrenaline, would not respond to oxytocin, but later *in vivo* work by Adler, Bell and Knox (1944) has shown that the cervix does react to oxytocin, although the doses required are usually larger than those needed to contract the uterus.

The present investigation has been carried out in conjunction with Professor W. C. W. Nixon and Mr. R. J. Fitzpatrick (1951), and its aim has been to record simultaneously the activity of the cervix and corpus of the human uterus and their response to drugs. External recording methods are unsuitable for this purpose since they do not register the movements of the cervix. We therefore used specially constructed two-way or three-way catheters with attached balloons by means of which intracervical and intra-uterine pressures could be recorded concurrently.

The observations were made before evacuation of the uterus in 24 patients whose pregnancy was being terminated in the first or the second trimester.

Contractility of the cervix.—The records show that the cervix can contract rhythmically, sometimes spontaneously but more often after the administration of drugs, particularly those of the ergometrine series. Contractions of the cervix usually followed those of the uterus but in some cases were completely dissociated from those of the uterus.

Action of ergometrine.—The most characteristic effect of ergometrine and methyl-ergometrine was stimulation of the cervix with or without corresponding stimulation of the corpus.

Action of oxytocin.—Intravenous injections of oxytocin produced contractions of the corpus even in the earlier stages of pregnancy, but the reactivity of the corpus to oxytocin increased after the first trimester. The cervix did not react consistently to oxytocin. In some experiments the cervix was contracted by oxytocin; in others it did not respond; and in yet others it apparently relaxed. Intravenous injections of oxytocin produced a marked transient fall in blood pressure.

Comparison of action of oxytocin and vasopressin.—Vasopressin powerfully stimulated the corpus. Its activity in this respect was equal to that of oxytocin in the first trimester, and about twice greater than that of oxytocin in the second trimester.

The main conclusion of this work is that contractions of the human cervix may be influenced by drugs and that the actions of drugs on corpus and cervix may be different.

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The Activity and the Pharmacological Reactivity of the Cervix and Body of the Uterus in Ruminants

By R. J. FITZPATRICK, B.Sc., M.R.C.V.S.
Department of Pharmacology, The University, Bristol

VERY little experimental work has been published concerning the contractility of the cervix. Newton (1934, 1937) and Bonnycastle and Ferguson (1941), made *in vitro* experiments whilst Adler, Bell and Knox (1944) have used an *in vivo* technique suitable for work with laboratory animals. Recently (1949), Karlson in Sweden has extended the observations of Moir (1934) and of Woodbury and his colleagues (1947), in women. The experiments about to be described were performed on ruminants using a technique essentially similar to that just described by Dr. H. O. Schild. These animals are particularly suitable for studies of this nature since the structure of the cervix is such that it is virtually impossible for pressure changes in the cavity of the uterus to be transmitted mechanically to the cervical balloon. Thus any affects ascribed to the cervix can be accepted as such without the possibility of their being a mechanical reflection of pressure changes in the uterine cavity.

The principal interest of these experiments to the obstetrician will lie in the support they give to those who postulate that the cervix may show activity dissimilar to that of the corpus.

Recordings were made from cows, sheep and goats in the second half of pregnancy and in the non-pregnant state. Many of the observations using non-pregnant animals were made after the administration of an œstrogen, progesterone, or thyroxine. Sheep and goats were placed in dorsal recumbency under nembutal or cyclopropane anæsthesia. Cows were restrained in the normal standing posture using extreme posterior epidural anæsthesia.

In rather more than half of the experiments the spontaneous activity and the reactivity to drugs were similar in cervix and corpus. However in a very substantial number of recordings, differences of behaviour between cervix and corpus were noted. The most interesting differences were as follows.[1]

Differences of timing and of direction.—The spontaneous contractions from the two zones were very often asynchronous. Either zone could contract first followed by the other after an interval ranging from five seconds to two or three minutes. This interval varied greatly during the course of each experiment. It mattered very little whether the cervix or the corpus was contracting first since in many experiments the order of contraction would change repeatedly. In some cases the cervix and corpus were contracting at the same rate but were completely out of phase so that the relaxations of one were synchronous with the contractions of the other.

Differences of amplitude of contraction.—There was no constant association between the pressure recorded in the cervix and that in the body of the uterus, sometimes that in the cervix being greater and at other times, during the same experiment, the reverse was observed. Moreover the amplitude of spontaneous contraction recorded by each balloon varied during the course of each experiment. These variations were completely independent for the two zones, short periods of powerful contractions, or of inhibition occurring in one zone whilst the other continued to contract as regularly as before.

When the results of different experiments were compared further dissimilarity was found. For instance, in recordings made in pregnant animals the spontaneous cervical contractions were more powerful than those of the body, whereas under different hormonal conditions the reverse occurred.

Differences of frequency.—In the majority of experiments each contraction of one zone was followed by a contraction from the other zone. Nevertheless a substantial number of recordings showed unequivocal differences in the rates of contraction of cervix and corpus, the ratio being as great as 6 : 1 on some occasions.

Differences of duration of contraction.—Both spontaneous contractions, and those induced by drugs were frequently found to be more prolonged in one zone than in the other. Such differences occurred most frequently after the administration of adrenaline or one of its homologues, when the stimulation of the cervix greatly outlasted that of the corpus. Schofield (1949), and Adler *et al.* (1944) have described similar effects in laboratory animals.

[1]Kymograph tracings were shown to illustrate these points.

Differences in response to drugs.—The actions of oxytocin, vasopressin and ergometrine were studied closely so that the responses in ruminants could be compared with those in humans. In addition a large number of drugs which could not be given to women were administered to the ruminants. These compounds included a series of sympathomimetic amines and a group of drugs with spasmolytic activity. In all cases drugs were injected into the external jugular vein using a drip technique.

With the majority of drugs, whether the response was motor or inhibitory, there was no difference between cervix and corpus. A few drugs, however, produced responses in which marked differentiation occurred. Contraction (or inhibition) of one zone was in these cases accompanied by either a lack of response or by inhibition (or contraction) of the other zone. Undeniable relaxation of the cervix accompanied by contraction of the corpus was recorded after the use of the sympathomimetics "Cobefrine", "Benzedrine", "Ephedrine", and "Butanefrine" and certain other compounds[1]. Of these drugs only two—"Cobefrine" and "Benzedrine"—produced this effect in more than two animals, and even with these compounds the responses were not always of this nature.

Although these results using drugs appear to be too inconsistent to be of value, it must be remembered that the differentiation of cervix and corpus might not be a question of absolute difference of response to a drug, but rather a difference of sensitivity. Such a suggestion is in keeping with the findings of previous workers (Newton, 1934, 1937; Bonnycastle and Ferguson, 1941; Adler *et al.*, 1944). Further this type of differentiation was shown to exist by our observations on women at University College Hospital (U.C.H.) as Dr. Schild has described. In pregnant ruminants evidence was obtained that the cervix responds to lower concentrations of ergometrine than does the corpus. Thus the threshold concentration of the sympathomimetic drugs necessary to elicit responses may be different for cervix and corpus. In these experiments drugs were being used which have not previously been administered to ruminants and the dosages adopted were to some extent empirical. Possibly the correct dose for eliciting different responses from cervix and corpus was given only in relatively few experiments. This would explain the apparent inconsistency of the results, and gives grounds for continuing this type of research with the object of finding a drug suitable for use in certain types of cervical dystocia.

There were some differences in the results obtained in ruminants as compared with those in humans. When given to pregnant ruminants ergometrine almost invariably produced a greater stimulation of the cervix than of the corpus. This is very similar to the action in pregnant women.

With posterior pituitary hormones, however, there was no such agreement. Several earlier workers have suggested that in pregnancy the cervix of various animals (including goats) is very much less sensitive to oxytocin than is the corpus and our results at U.C.H. showed that oxytocin produces a greater stimulation of the corpus than of the cervix in pregnant women. In pregnant ruminants, however, it was found that the response of the cervix to oxytocin was at least as great as that of the corpus.

With vasopressin the results in sheep were very different from those in humans. Whereas our work at U.C.H. showed that oxytocin and vasopressin were, at some stages of pregnancy, approximately equiactive, in pregnant sheep oxytocin was in all cases found to be at least ten times as active as vasopressin.

These variations emphasize the difficulties of applying the results of experiments obtained in one species to others. The detailed results of the ruminant experiments will be of only small interest to the obstetrician, but they are of importance in one respect, namely, that they have provided us with further fresh evidence in support of the principle that the cervix can show muscular activity independent of that of the body of the uterus.

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[1]Two new compounds, kindly supplied by Dr. F. Bergel of Roche Products, also gave this type of response.

Anatomy of the Human Cervix in Pregnancy

By P. E. Hughesdon, M.B.

The human cervix uteri consists of an outer quarter, which is mainly muscular, and an inner three-quarters, which is mainly collagenous. This arrangement is present at birth and persists throughout life.

The outer muscular layer forms a complete investment of the cervix and links up with the corporeal muscle above and the vaginal muscle below. Its fibres run in every direction. They are separated by broad septa of loose collagen, but are mature and certainly capable of function. In hysterectomy material this layer is apt to be obscured by post-vital retraction. The inner bulk of the cervix consists of dense tangled collagen, in which are scattered many immature, probably non-functional, muscle fibres. These are small, narrow, poorly staining, and similar to the fibres of a small myoma. They run in every possible direction, but are mainly longitudinal and radial under the mucosa and circular further out.

During pregnancy collagen fibres are progressively reabsorbed and replaced by fluid. The process is of course never complete; it starts under the portio and spreads gradually upwards to the internal os. The resulting softening probably allows the outer mature muscle (which hypertrophies somewhat during pregnancy) to influence cervical diameter. With the unfolding of the isthmus there develops in the region of the internal os a local accumulation of circular muscle which probably acts as a compressor. The immature muscle of the inner bulk of the cervix undergoes a temporary hypertrophy and hyperplasia; in the latter part of pregnancy it remains stationary or involutes.

Towards term the cervix consists of a central mass of non-contractile tissue—immature muscle, collagen and fluid—with mature muscle layers, transmitting the pull of the upper segment, applied tangentially across the top and down the side. The retardation or advancement of these two layers relative to one another produces variation in the anatomical pattern during taking-up and dilatation. Precocious movement of the outer muscle layer, attached down the side of the cervix, tends to open it from below; and there is evidence that this is associated with severe dystocia. Precocious movement of the upper muscle layer, attached across the top of the cervix, was seen in a case of habitual abortion at the sixth month of pregnancy. These two aberrations are interpreted as resulting respectively from excessive strength and excessive weakness of the circular muscle round the internal os.

[Slides were shown illustrating these points.]

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(As no reviewing is undertaken in the "Proceedings" this list is the only acknowledgment made of books received for review)

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Section of Orthopædics

President—A. T. FRIPP, F.R.C.S.

[*March* 6, 1951]

The Relapsed Club Foot

PRESIDENT'S ADDRESS

By A. T. FRIPP, F.R.C.S.

THE treatment of relapsed club foot is a complex problem, but there has been a tendency to over-simplify it—for example by advocating either forcible manipulation or early arthrodesis as a routine in the difficult case.

Modern treatment started with W. J. Little (1839) who introduced tenotomy into England in 1837. He was able to produce a plantigrade foot with little apparent difficulty, and we may well feel that something has been lost in spite of the advantages under which we work now compared with one hundred years ago.

Two points stand out in his book—the infinite care with which splints were fitted, and the gentleness of his manipulations. He wrote: "The slightest pressure of the instrument will suffice to overcome the deformity provided attention be daily paid. The surgeon must bear in mind that he must not always expect to restore the foot rapidly to its natural position. He must guard against violence."

The basic problem is the correction and maintenance of correction of the 4 constituent deformities: equinus, inversion of the heel, plantaris, adduction of the forefoot.

A bad equinus is very difficult to deal with. There is a disproportion between the tibio-fibular mortice and the talus, so that if the Achilles tendon is lengthened the amount of improvement may be quite disappointing. If force is used, the hindfoot remains in equinus and the mid-tarsal joint gives, leaving a rocker foot.

A persistent inversion of the heel is also troublesome. In theory this should be completely corrected by a triple arthrodesis, but it is apt to recur even after an apparently satisfactory correction with subtaloid fusion. Forefoot adduction may occur at any or all of the following joints: talo-scaphoid, scapho-cuneiform or cuneo-metatarsal.

There may be only one of these present, but in a bad club foot they are all present with one predominating over the others, this one element presenting greater difficulty of correction and a greater tendency to recurrence. Therefore there is an almost limitless range of permutations—no two club feet are quite alike and there is no standard treatment that is applicable to all feet.

Other difficulties centre around the rigidity of the foot in the newly born infant, muscle imbalance, rotation of the tibia, and other congenital abnormalities below the knee.

Turning to possible lines of treatment there are three approaches:

(1) *Forcible manipulation and plaster.*—This is widely used, but I believe that it is unsound both in theory and in practice, and that the greater the force employed, the worse the treatment. To consider the theory first. There is a close analogy between congenital dislocation of the hip and the dislocation of the head of the talus out of its acetabulum with the scaphoid lying close to the internal malleolus and firmly held there by a thickened fibrous band, Parker's capsule. If a manipulation is to be successful the head must be reduced into the acetabulum and to achieve this in the foot the scaphoid must be moved into its correct position; but Parker's capsule is inelastic, and the result is that the position of the scaphoid remains unchanged, the internal scapho-cuneiform and cuneo-metatarsal ligaments, being relatively weak, are stretched and a spurious correction occurs at the mid-tarsal joint.

In practice this is what happens in a large proportion of cases. The number of relapses is high and often the case notes record one series of manipulations followed by a second and a third at intervals of a few months. Each manipulation results in some trauma, with an increase in fibrosis and a progressively rigid foot. There is a vicious circle of increasing violence necessary to overcome increasing rigidity. Forcible manipulation under an anæsthetic should be abandoned as useless and harmful.

FIG. 1.—Typical relapsed club foot. Scar of operation for elongation of tendo achillis is seen, but heel is raised and inverted.

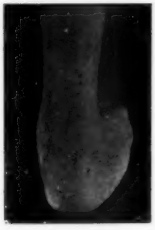

FIG. 2.—The same foot corrected by Kite's method.

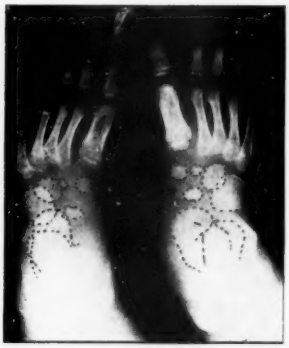

FIG. 3.—X-ray of normal (R.) and relapsed (L.) *Note*.—R.—separate outline of talus and os calcis, and scaphoid in front of talus. L.—talus and os calcis outlines superimposed. Scaphoid on inner side of talus.

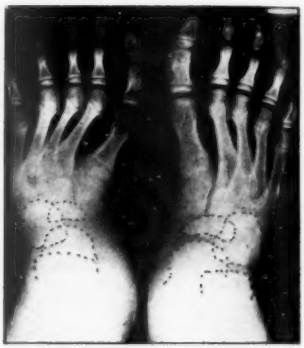

FIG. 4.—R.—normal. L.—scaphoid correctly placed, but talus and os calcis superimposed and forefoot deformity takes place at scapho-cuneiform joint.

(2) *Operations*.—Many operations have been devised, and it is not possible to consider all of them, but the results of many were bad and left the patient worse off. Theoretically it should be possible by removing enough bone in the course of a tarsectomy or triple arthrodesis to correct the residual deformity in any club foot, but in practice it does not work out that way, and a varus deformity can recur after X-ray evidence of sound fusion.

Of the soft tissue operations the "open correction" as described by Brockman is theoretically sound, as the division of Parker's capsule does enlarge the acetabulum and allow the head of the talus to be reduced into it. At the same time the scaphoid is brought round from the inner side into its correct position. But there is often some inversion of the heel as well, upon which the open correction has little effect and the liability to recurrence varies directly with the degree of this inversion.

The other soft tissue operation is the tendon transplant of tibialis anterior to the outer side of the foot, which is designed to deal with the muscle imbalance due to peroneal weakness. The transplant cannot secure any increased correction, it can only maintain correction already secured by other means, and therefore it is essential to consider carefully the timing of the operation. It must only be done *after* a complete correction has been secured. Properly used it is a very effective operation.

(3) "*Non-operative*" *treatment*.—There remains a group of children up to about eight years with a residual deformity and an ill-balanced foot, and I believe that the solution for the majority lies in the "non-operative" method described by Kite. By non-operative he means not only that there are no cutting operations, but no manipulations under an anæsthetic. It does not supplant operations when they are indicated, but it is applicable to most cases, and in cases which do require operation, it should be carried out first, as it makes operation easier and the results more certain.

There is no easy way of ensuring a good result in a difficult club foot; and this method demands a good deal of patience, as the time it takes may extend over several months. One buys function at the expense of time, but I think the investment is a good one. "The force used is limited to that which causes the patient no pain and if this is done there will be no damage to the joints. By the use of less force and more patience the feet can be corrected with a closer approach to normal function."

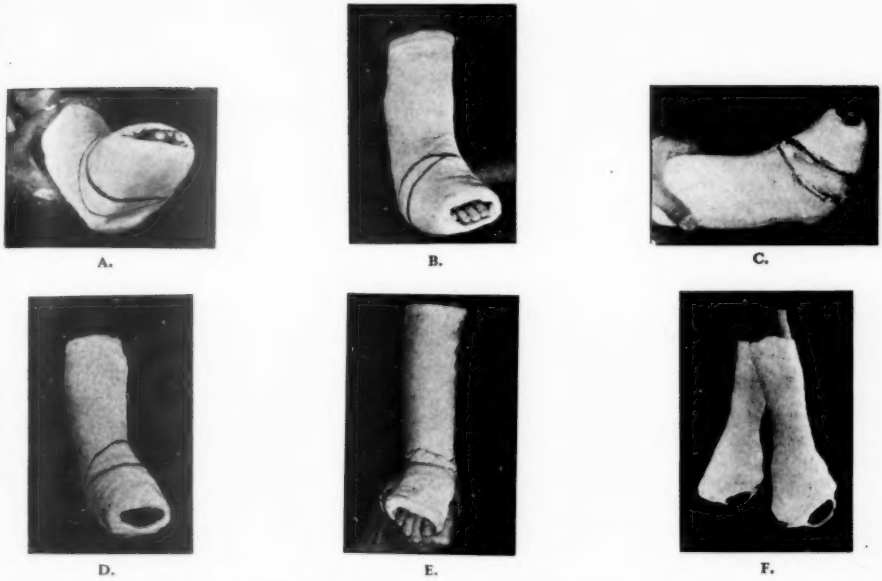

FIG. 5.—Kite method of correction. A and B varus wedge outlined. C, varus wedge removed. D, equinus wedge outlined. E, equinus wedge cut out and closed. F, Rockers applied. Feet are in well-marked equinus, as the varus is in process of correction.

The treatment is divided into four phases: (1) Correction of the varus. (2) Correction of the equinus. (3) Retention in an over-corrected position. (4) Follow-up treatment.

A padded cast is applied to the foot with as much correction as is possible without causing pain. One week later a wedge is cut in the plaster with the apex on the inner side and the base on the outer side. It is found that by gentle and painless manipulation the gap can be closed and the two sections of the cast are reconstituted by a fresh plaster bandage. The process is repeated three to four times at weekly intervals and then the cast is removed and a fresh one applied. This is continued until the mid-tarsal deformity and inversion of the heel are corrected. The equinus is then corrected by a series of wedgings, the apex of the wedge at the back of the heel and the base over the dorsum of the ankle.

The method is undoubtedly efficient and it causes a minimum of trauma to the foot, and a minimum of pain and mental upset to the child.

It is important to determine when the varus deformity has been adequately corrected. Clinically the degree of correction can be judged by the tendency of the foot to turn in again. If there is such a tendency, correction is probably incomplete and further varus wedging is necessary, but X-ray control is also important. Firstly the scaphoid should be directly in front of the talus and not tucked round the inner side. Secondly in the A.P. view of a normal foot the head of the talus and the anterior process of the os calcis appear as two separate shadows, the os calcis lying to the outer side. In an uncorrected club foot the os calcis swings inwards and the two shadows are superimposed. It follows from this that correction is not complete until the two shadows have regained their normal relationship. In the lateral view with the foot dorsiflexed, the head of the talus and anterior process of os calcis are on the same level; but until the equinus has been completely corrected, the os calcis is displaced posteriorly, and therefore correction should go on until the normal relationship has been attained.

The third stage—retention in the corrected position—is a problem on its own, as irons, night splints, shoes or wedges are quite useless in preventing relapse. Kite uses a retentive plaster for some months, but this prolongs the period of immobilization and in many cases a tendon transplant offers a quicker and equally efficient method of retention. Peroneal weakness is so often a factor in causing relapse that a transplant may well be necessary even after a period of retentive plasters.

It is quite striking how a foot which feels stiff and resistant softens up after a week in plaster. The successive wedgings slowly bring about a mid-tarsal correction and simultaneously the inversion of the heel yields until the foot as a whole loses its varus tilt. One should mould the plaster round the heel as much as possible, but it seems rather that the hindfoot follows the forefoot, and the mid-tarsal wedge alone is sufficient to correct both parts of the foot. Herein lies the great advantage of this method over the soft tissue operation which has no appreciable effect on correcting the varus heel.

It is essential to correct the mid-tarsal and inversion deformity before attempting to deal with the equinus, and this is one of the basic principles in the treatment of club foot at any stage. If it is neglected the scaphoid is forced up on the inner side of the foot, so that a spurious correction is obtained and is followed by relapse.

In assessing after-results one must remember that the patient is the final judge of whether he has a good foot, and there is quite a difference between theory and practice. Occasionally one meets a patient whose foot by our standards is a thoroughly bad result, and yet he is quite satisfied with it. But isolated cases are no justification for allowing such deformities to occur or for failing to give the patient the best possible foot.

Putting oneself into the patient's place, what would we want? We should want to be free from pain, to wear ordinary shoes, we should want to be able to play games or to dance, to earn a living or to look after a house and bring up a family; and—in the order of their importance—the factors in giving good function are: (1) Equal distribution of weight. The foot must be plantigrade. (2) Shape and size. (3) Suppleness. (4) Muscle balance. (5) Muscle power.

Freedom from pain means chiefly freedom from corns and callosities. The ability to wear ordinary shoes is important both economically and æsthetically, and in a woman demands a foot of near normal shape and of a size approaching the sound foot.

Suppleness and muscle balance must be considered together, for one is of no use without the other. Suppleness requires freedom from the fibrosis of forcible manipulation, freedom from arthritis and freedom from fusion, and if these can be combined with effective muscle balance, the patient has a good foot. But muscle balance is essential and while there is a better chance that a supple foot will stand up to the strains of life than a rigid foot, a rigid plantigrade foot is better than a supple ill-balanced one. Muscle power, and especially that of the calf, is relatively unimportant.

It may not be possible to achieve all these factors in every foot, but the method of treatment which achieves the greatest proportion will be the most successful. Excluding forcible manipulation, which I should like to see discarded entirely, the choice lies between operation and the Kite method, or a combination of the two; and I believe that this—the non-operative—is the method of choice. It should be used as a preliminary in every case of relapsed or incompletely corrected club foot. Often operation can be avoided and in all other cases it will simplify the problem of operation and leave only one residual deformity, which is much easier to deal with by operation, in place of the combination of deformities which may not be amenable to any one operation.

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Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*April* 19, 1951]

Chronic Disseminate Lupus Erythematosus with Lichenoid Lesions.—BENJAMIN SCHWARTZ, M.D.

Mr. F. T., aged 63, who had had no previous skin disease, first came under treatment in 1941 for undoubted chronic lupus erythematosus involving an area on the left side of the face. Between 1941 and 1950 he was treated with carbon dioxide snow, quinine, sulphonamides, arsenic, bismuth and gold. Three separate courses of gold were given (a total of approximately 2·5 grammes). There was, however, a gradual spread of the condition to involve the buccal mucosa, lips and scalp.

In June 1950 a new eruption appeared rapidly during two to four days, involving areas on the arms and legs which hitherto had not been affected by the disease. Beyond some mental anxiety the new lesions caused no constitutional disturbance, nor at the start did they irritate; some irritation is reported now. Because of the sudden spread further treatment with gold was commenced, but this, the patient states, produced more new lesions every week. The course of gold was stopped after eight injections and he was transferred to St. George's Hospital for possible cortisone or ACTH treatment under Dr. Stephen Gold. His admission there was precipitated by the unrelated occurrence of a hæmorrhagic pleural effusion. Routine investigations indicated that there was no systemic involvement of lupus erythematosus.

Present condition.—(1) Scarred lesions of lupus erythematosus on face, lips and scalp (Fig. 1).

(2) Irregular verrucous plaques with firmly adherent scales resembling lichen planus hypertrophicus scattered over the body but chiefly involving the backs of both hands and forearms (Fig. 2), the left leg and the scalp. There was a lesion unmodified by treatment on the left thigh.

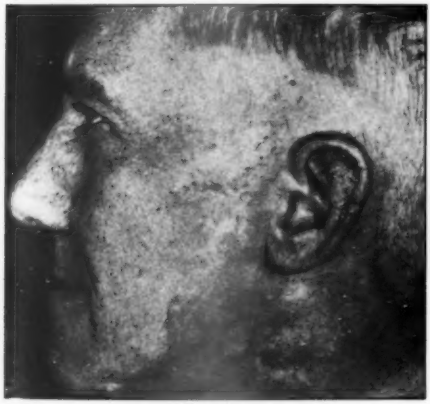

FIG. 1.

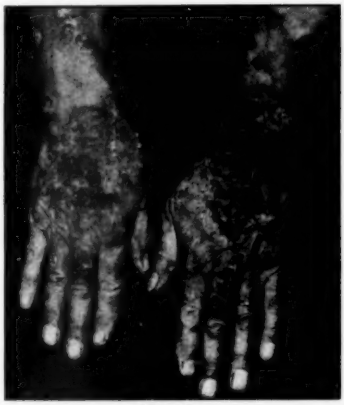

FIG. 2.

(3) A generalized slaty-grey pigmentation on a sallow skin is most noticeable on exposed areas, and is seen especially on the neck and ears where, following confinement to bed for the past three months, the distinction between exposed and unexposed areas is probably more marked than is natural.

(4) Local lesions have markedly hyperpigmented edges.

(5) A small bullous lesion developed on the left index finger four days ago. This is the first such lesion which has occurred throughout the history of the disease.

Investigations.—W.R. and Kahn reaction, negative. Blood count, E.S.R., E.C.G., normal. Serum: total protein 7·5 grammes; albumin 3·2 grammes; globulin 4·3 grammes per 100 c.c.

Histology of lichenoid lesion.—Considerable hyperkeratosis, follicular plugging, flattening of the dermo-epidermal junction and a diffuse and perivascular cellular infiltrate—features of chronic lupus erythematosus. (A similar conclusion was reached by Dr. Haber when he examined a section in November 1950, before the patient was transferred to St. George's.)

Treatment.—The lesions on the right forearm have been treated with carbon dioxide snow during the past month with considerable improvement. Local application of salicylic acid to the left arm has had little effect. An isolated lesion on the left arm was treated with X-rays (4 doses of 100 r), which resulted in a very great increase in pigmentation.

Comment.—The histology in this case is somewhat doubtful. Lupus erythematosus is the most likely diagnosis, but it is difficult to distinguish the section from that of lichen planus. If this *is* a case of lupus erythematosus, the clinical appearance of the lesions is somewhat unusual; in view of the pigmentation, the fact that he has had gold and that there was so much spread during the last course of gold, this condition may be a lichenoid gold eruption rather than lupus erythematosus. The recent occurrence of a bullous lesion is also more in favour of lichen planus rather than a lupus erythematosus. I hoped to find gold in the tissues and a small piece was subjected to spectroscopic examination, but the evidence for the presence of gold was not very convincing.

Mr. G. B. Dowling: I have an identical case, a patient who presented herself two or three years ago with a reddish scar on the scalp. We could not make any diagnosis on it, but after a time she developed follicular horny plugging round the scar and one thought that the condition must be lupus erythematosus. She had no gold or other metallic treatment and carried that diagnosis for a long time; however, comparatively recently she developed lichen planus of the hypertrophic warty type on the forearms. The lesion in her scalp is not quite so lumpy as the scalp lesion in Dr. Schwartz's case but the change is of the same type. It is not always easy to distinguish lupus erythematosus of the scalp from lichen planus and I would suggest that the present case has, throughout, been one of lichen planus.

The President: I have seen a case of quite typical discoid lupus erythematosus which became disseminated and systemic. The lesions gradually assumed the features characterizing the present case: great thickening of the skin and a warty surface, and, in places, discrete round warts. There were no small lesions suggestive of lichen planus. My case had been given bismuth and this may have been an important factor in inducing this lichenoid metamorphosis of the lupus erythematosus.

Dr. H. Haber: I have seen a case at St. John's Hospital when it was diagnosed clinically as lupus erythematosus. When treated with gold the patient developed a generalized lichenoid eruption which both clinically and histologically showed overlapping features of lichen planus and lupus erythematosus. A few months later the patient's condition cleared up completely, but presented on his legs typical lichen planus which was confirmed histologically.

Dr. R. D. Moyle: I think the speaker omitted to mention a polygonal flat-topped papule just above the verrucose area on the forearm, similar in colour to lichen planus, and white pin-point lesions on the buccal mucosa. I feel quite sure that there is lichen planus on the left forearm and in the mouth.

Lupus Erythematosus.—ARTHUR ROOK, M.D., and P. J. B. THOMAS, M.B.

D. W., aged 24, a lorry driver, first attended the Out-patient Department on 27.2.51. He suffered from scarlet fever at the age of 8 and is said to have had anæmia at 13. At 21 he had an appendicectomy. He has never suffered from any skin disorder. His mother has bronchitis but his father and younger brother are in good health. Two uncles and an aunt died of pulmonary tuberculosis.

In 1944 at a fair in Aldershot his left forearm was tattooed with an elaborate design in blue with roses in red. In January 1951 red patches suddenly appeared on both cheeks and enlarged rapidly over a period of a few weeks. At precisely the same time he noticed moderately severe irritation in the tattoo. This irritation has persisted. After about a week he noticed that the red areas in the tattoo were becoming raised and warty (Fig. 1), and they became increasingly so during the next three weeks. There has been no change in the facial or arm lesions in the last six weeks. The blue areas in the tattoo have not irritated at any time. He had no upper respiratory infection or any constitutional symptoms either immediately preceding the appearance of the skin lesions or subsequently.

On examination.—A healthy young man with no discoverable physical abnormality in any system other than the skin. On both cheeks there are discoid patches of lupus erythematosus. In the tattoo there is no detectable change in the blue areas, but the roses are elevated and warty.

Investigations.—27.2.51: X-ray chest: No abnormality detected. White blood count 27.2.51 within normal limits. E.S.R. 9 mm. in one hour (Wintrobe). W.R. negative. Patch test: 2% ammoniated mercury: very strongly positive.

Biopsy (Dr. I. W. Whimster).—*Arm* (a rose was excised): (Section 1) Severe generalized, irregular epidermal hyperplasia, subepidermal œdema and vascular dilatation and focal infiltration by lymphocytes (Fig. 2). There is much pigment in the upper layers of the dermis which by transmitted light appears black but by incident light orange-red. This pigment is in colour identical with vermilion (red mercuric sulphide).

(Section 2) (not illustrated) Similar changes to (1) except that in the centre of the section there is no pigment and in this area there is no inflammation or hyperplasia. In the inflamed areas there is mild fibrinoid degeneration of the sub-epidermal connective tissue.

In both sections the inflammation and hyperplasia are compatible with the diagnosis of lupus erythematosus. Although the pigment appears to have the same distribution in the skin as the inflammatory reaction, the inflammation is not centred round the pigment particles themselves.

Face: The epidermis is flattened and there is keratotic plugging of the follicles: there is a marked lymphocytic infiltrate mainly around the skin appendages (Fig. 3).

Comment.—The technique of tattooing commonly practised in civilized communities consists of the introduction of pigment particles into the dermis with a special electric needle. Carbon in the form of Chinese or Indian ink is used to obtain the blue colours in the design and cinnabar (mercuric sulphide) for the red. The use of other pigments seems to be rather uncommon (Mathews, 1947). The delayed development of sensitivity to cinnabar has often been observed, an eczematous reaction limited to the red areas of the tattoo appearing after an interval of a few months or after many years. In some cases the reaction in the tattoo has appeared only after sensitivity to mercury has been accidentally induced by the application of a mercurial preparation to some other area of the skin, but in most cases it has developed spontaneously. Usually sensitivity persists indefinitely, but Sulzberger *et al.* (1944) have reported a case in which the sensitivity diminished after a few weeks.

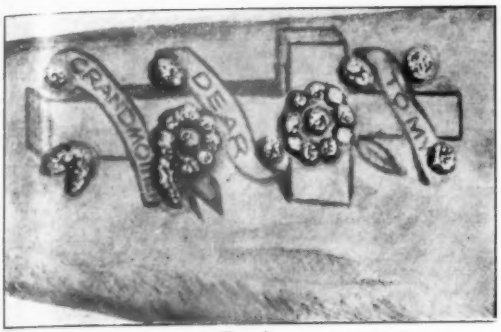

FIG. 1.

FIG. 1.—Forearm showing the warty appearance of the red areas of the tattoo. (Photograph of water-colour sketch by Miss J. M. Williams.)

FIG. 2.—Biopsy of warty lesion of forearm.

FIG. 3.—Biopsy of facial lesion.

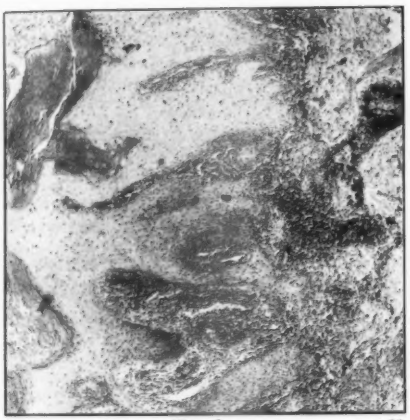

FIG. 2. × 33

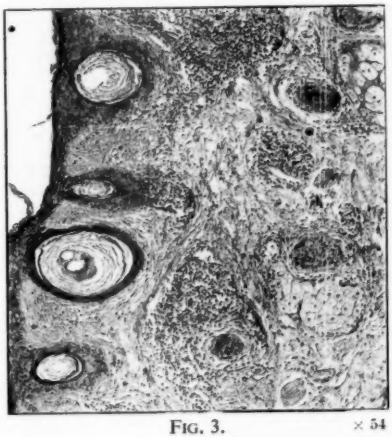

FIG. 3. × 54

Madden (1949) describes a case of a man of 36, tattooed four years previously, who developed lupus erythematosus simultaneously on the face and in the red areas of his tattoo. On two occasions exposure of the face only to sunlight was followed by a flare of the lesions on the face and on the arm which had remained covered.

There are two possibilities to be considered. Either development of sensitivity to cinnabar is an essential pathogenic factor in provoking the lupus erythematosus reaction or lupus erythematosus provoked by some unrelated and unknown factor localizes at the site of a pre-existing low-grade, inflammatory focus as psoriasis or lichen planus may do. However, it is of interest that when these latter diseases develop in tattoos, they are not localized to the red areas.

The results of patch tests with cinnabar and other mercurial compounds are inconsistent even in the simple eczematous reactions in tattoos. McKenna (1948) has suggested that some intracellular pigment particles dissociate and form organic compounds which act as haptens.

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SULZBERGER, M. B., KANOF, A., and BAER, R. L. (1944) *U.S. Nav. med. Bull.*, **43**, 889.

Dr. **A. Lyell:** Had this patient used any mercurial preparation on the face before the lupus erythematosus occurred?

Dr. **I. R. Marre:** Two years ago I had a patient with a granulomatous eruption of the red areas of a tattoo mark on his arm. He had also a dermatitis of the beard area and it turned out that he used a mercurial shaving cream. The granulomatous areas on the arm came up together with the eruption of the face, but the face subsided when he stopped using the mercurial cream. The granulomatous red areas of the tattoo mark were excised. He was strongly positive to mercury ointment patch tests.

Dr. **A. J. Rook:** POSTSCRIPT 28.5.51.—The patient was not using a mercurial cream.

Dermatomyositis in a Patient with a Past History of Carcinoma of the Ovaries.—L. FORMAN, M.D.

Mrs. R. S., aged 55. Two children.

1943: Ovaries removed with uterus for papilliferous carcinoma of ovaries.

March 1950: Fatigue and lassitude, with stiffness of arm and trunk. This became very severe by October 1950: was unable to dress herself and movement was very painful. At that time, erythema noted on sides and back of neck, face, left ear, front of chest, shoulders and outer aspect of upper arms. Dorsal aspect of terminal phalanges became painful, erythematous, with telangiectases which were longitudinal and not punctate as in lupus erythematosus.

There is a diffuse erythema of scalp and orbits with a cyanotic tinge, and fullness of eyelids; erythematous areas on sides of face, chin and back of neck; a plaque on the shoulder, yellow with a slightly mamillated surface recalling pseudoxanthoma elasticum; an erythematous patch with small areas of superficial atrophy and crust on front of chest. The subcutaneous tissue thickened under the erythema of upper arms.

Musculature generally weak; most easily demonstrated on elbow extension and hip flexion. No reflex or sensory changes. Sternal puncture did not reveal any Hargraves' cells, nor were any seen in blister produced on skin by cantharides.

Section (Erythematous area on shoulder).—Epidermis thinned to few layers of cells; vessels of papillary and subpapillary layers of cutis dilated with slight lymphocytic surround; connective tissue of papillary bodies and narrow band below, œdematous, and fibres form a fine reticulate pattern.

From another area, similar appearance with more œdema of epidermo-dermal junction.

Muscle biopsy from deltoid muscle—Collection of lymphocytes between the muscle bundles; muscle fibres show œdema and longitudinal separation.

Comment.—This case is of interest because of the history of ovarian carcinoma. In my opinion, the association of dermatomyositis with neoplasia is not fortuitous. It has been referred to by S. Rothman (1925) *Arch. Derm. Syph., Berl.*, **149**, 99, and R. Bezecny (1935) *Arch. Derm. Syph., Berl.*, **171**, 242. Further, dermatomyositis is only one of the erythematous reactions associated with carcinoma.

The following examples have been observed personally:

(1) Man aged 65, with general muscular weakness and difficulty in swallowing. Spider nævi in large numbers on face, forehead and upper chest, with palmar erythema. Death from heart failure. At post-mortem, large gland found in mediastinum which, on section, proved to be oat-cell carcinoma.

(2) Man aged 58. Numerous spider nævi and palmar erythema. Post-mortem: carcinoma of bronchus and massive infiltration of liver.

(3) Man aged 39. Localized erythema of exposed areas of scalp, ears, face, backs of hands and chest. Areas on backs of hands hyperkeratotic and suggestive of lupus erythematosus. Clinical investigation showed no evidence of carcinoma, but blood and mucus in stools. One and three-quarter years later patient was found to have carcinoma of abdomen.

(4) Woman aged 68. Diffuse erythema of face, scalp, and limbs with telangiectasia and superficial atrophy; no muscle weakness: carcinoma of cervix uteri demonstrated a month after she was first seen.

(5) Characteristic dermatomyositis with erythema of face, limbs, and trunk and muscle weakness. Examples—Woman aged 60 with carcinoma of left breast. Woman aged 51 with carcinomatous glands and deposits in mediastinum; site of primary unknown.

In the case described by Bezecny, there seemed to be no doubt about the relationship between dermatomyositis and carcinoma of ovaries. Removal of the ovaries was followed by dramatic improvement in the muscle weakness within a few days. The dermatomyositis had been present a year before operation.

The relationship between the changes described and carcinoma is a matter of conjecture. Probably the skin changes are not due to toxic substances produced by the carcinoma, because two patients (5, above) showed clinical improvement of the erythema and muscle weakness although the carcinomata were progressive and inoperable. Alteration in the hormone level of the blood might explain the telangiectases and erythematous element of the reaction. Similar changes have been seen with pregnancy and in individuals with severe liver disease. One patient described (2, above) had a grossly infiltrated liver, which could quite well have given rise to changes in the blood level of œstrogens and androgens. With carcinoma of the genital organs, breasts, ovaries and uterus, significant deviations in the blood hormone level could quite well occur only during a phase in the history of the carcinoma.

Dr. S. C. Gold: There may be hormonal influence in some of these conditions. It is well known that rare cases of systemic lupus erythematosus have been improved by removal of the ovaries, yet recently I have seen two women in whom there was an undoubted association between oophorectomy and development of lupus erythematosus. The first has since died and the second one is now in a remission stage; it does seem that a critical balance of hormones may be an influencing factor on the development of these so-called collagenoses.

Dr. J. T. Ingram: I have recently seen at a Sheffield meeting such an erythema of the face associated with a neoplasm in the chest. Eighteen months ago Dr. F. F. Hellier had a patient with advanced dermatomyositis who is now dying from carcinomatosis though the dermatomyositis has cleared. These experiences emphasize that dermatomyositis is a symptom and not a disease. It is, however, interesting to consider the significance of the malignant reticuloses which sometimes develop from cases of poikilodermatomyositis.

There may be a close association between poikilodermia and hormonal imbalance.

Dr. R. E. Church: I am reminded of a man who was admitted to Addenbrooke's Hospital, Cambridge, with a typical attack of dermatomyositis. He had a fever, œdema of the face and an erythematous rash of the face and dorsa of the hands similar to Dr. Forman's case. There was marked weakness and wasting of the muscles, particularly of the shoulder girdle which progressed after the rash faded. About four months from the onset of his illness he developed a cough and abnormal signs in the chest. An X-ray, which at the beginning of his illness showed no abnormality, now showed a carcinoma of the bronchus from which he died two months later.

The following cases were also shown: **Pigmentary Dermatosis.**—Dr. BENTLEY PHILLIPS. **Benign Familial Pemphigus (Gougerot, Hailey-Hailey).**—Dr. L. FORMAN and Dr. H. HABER. **Adenoma Sebaceum.**—Dr. C. D. CALNAN for Dr. R. T. BRAIN. (These cases may be published later in the *British Journal of Dermatology*, together with the Meeting on *May* 17, 1951.)

Section of Radiology

President—RALSTON PATERSON, M.C., C.B.E., F.R.C.S., F.F.R., D.M.R.E.

[*October* 20, 1950]

DISCUSSION ON MYELOGRAPHY

Dr. Hugh Davies: The history of myelography goes back to 1921, when Lafay experimented with the "treatment of epidemic encephalitis by strong injections of iodized oil". Sicard and Forestier, "finding that this substance was not especially irritating to the meninges and was opaque to the roentgen ray, injected it and demonstrated spinal cord compression". After the publication of their paper in 1928, myelography became fairly widely used, but it was not until the advent of improvements in equipment, especially that of the tilting couch, that the procedure became capable of giving the results obtainable today.

Contrast medium.—Lafay's original iodized poppy seed oil, Lipiodol, was found to produce in many cases irritative reactions in the meninges. Experiments were made by various workers with other iodized vegetable oils, but none was wholly free from irritative effects, and there was found to be a definite relation between the amount of contrast medium used and the degree of the reaction (Odin and Runström, 1928).

Thereafter there was some reluctance to use myelography, except as a final diagnostic court of appeal and then only with small quantities of contrast medium, until the demonstration of protruded disc material as a cause of sciatica caused a sudden broadening of its field of use. Controversy as to the risk of reaction continued and led to the trial of air myelography in the lumbar region. In this country, the cutting off of the source of supply of lipiodol during the war encouraged this. In 1944 Ramsey, French and Strain presented a new opaque medium, ethyl iodophenylundecylate. This substance is oily and is very slowly absorbed. Finally Arnell, who with Lidström had first suggested the use of Abrodil as a water-soluble contrast medium in 1931, published in 1944 a monograph describing its use in combination with spinal anæsthesia. This method has found wide acceptance, but its use is limited to the lumbar region.

There are, in my opinion, grave doubts as to the desirability of injecting Diodone into the subarachnoid space. A spinal anæsthetic is necessary and this is not without its own risks; because of this the method cannot be used except in the lumbar region; also diodone is an irritant and, while the anæsthetic may mask the immediate results, there have been reports of after-effects persisting long after the presumed absorption period of the contrast medium; finally, it seems to me that any lesion which is demonstrable by this method can be demonstrated by one of the oily media.

Air myelography has the great advantage of a completely resorbable, non-irritant contrast medium. It has the disadvantage of being applicable as a rule only to the lumbar region, though I am informed that in Sweden work is being performed on air myelography by cisternal puncture with the patient's head lowered and complete replacement of the spinal fluid. In my experience the contrast obtained is often inadequate to reveal small defects in the air column, especially in the antero-posterior view, even with careful stereoscopic technique. Camp sums up the situation by saying that his experience of air myelography over many years has convinced him that it is not a procedure to be recommended for the casual or inexperienced examiner. He goes on to say, however, that he feels that in lumbar lesions, with intelligent appreciation of its limitations, it has its uses.

Of the oily media lipiodol is more viscous than Pantopaque and slightly more opaque. It is therefore more easy to control its flow and to keep the column of contrast medium intact over the site of a suspected lesion. Camp in his Carman lecture of last year said that he felt that lipiodol had consistently given him more accurate information than pantopaque or any other agent, and that he felt it to be the medium of choice for the recognition of thoracic lesions. There is, however, evidence that there may be some meningeal reaction, even though only transient, to lipiodol, and if withdrawal of the medium to minimize the risk of reaction is contemplated, lipiodol presents greater problems owing to its viscosity.

Pantopaque has become, since its introduction, the contrast medium of choice in the U.S.A. and this country. Its disadvantage lies in its lesser viscosity, but it has the great advantage of causing no detectable reaction in the great majority of cases. In a series of 106 myelographies no symptoms or signs of reaction were noted after myelography with 6 c.c. of this medium, no attempt being made to remove it. Bering in 1948 was able to re-assess 26 of these cases; the remainder for various reasons were not available for a full examination. In most of these cases it was found that the medium had become fixed, in many partly in the basal cisterna. In no case, however, on full neurological examination, was any symptom or sign attributable to the contrast medium elicited. The fact of fixation of the medium suggests that some reaction must occur, but my experience leads me to feel confident that, except possibly in a case of unusually acute sensibility to iodine, ethyl iodophenylundecylate is the most generally useful medium for myelography.

Amount of contrast medium.—More mistakes have probably been made in diagnosis in myelograms by the use of inadequate amounts of contrast medium than from any other single cause. In the early days when it was realized that some meningeal reaction occurred, and Odin and Runström showed that the degree of reaction was related to the amount of lipiodol used, clinicians were not unnaturally anxious to use the minimal amount. I feel that 6 c.c. of contrast medium is essential in the average case. This is sufficient to allow visualization of the lumbar region over a length of at least two vertebral segments, and of the whole of the cervical region. I would agree that, where there is clinical or manometric evidence of a block, it may be reasonable to define its level by a smaller amount.

Route of injection.—Before tilting tables with adequate screening facilities became available, cisternal puncture was usually employed, with the patient sitting. The downward passage of the oil was followed by screening or

a series of films. With modern apparatus the lumbar route is in my opinion the better, except in the rare cases where it is necessary to define the upper limit of a space-occupying lesion.

Withdrawal of contrast medium.—It has been my practice for the past five years not to attempt to withdraw contrast medium except in the very few cases where a large quantity (10 c.c. or more) was used. Withdrawal involves either leaving the needle in situ during the examination, with some attendant risk, or a second puncture; in the majority of cases it also involves the patient in considerable discomfort from the sucking of nerve roots against the needle point, and I have more than once seen hæmorrhage produced. I feel satisfied that it is safe to leave any normal amount of contrast medium in situ.

Technique of examination.—In the ordinary case the contrast medium is introduced by lumbar puncture either on the X-ray couch or in the ward, care being taken that it should remain in the lumbar region. The patient is transferred to the prone position and is supported by padded shoulder rests. Position of the medium is controlled by screening and films obtained in the anteroposterior projection with the undercouch tube, and laterally with the overcouch tube swung to the side of the couch.

In this country we are at a disadvantage as yet in that we have no couch available which will provide a full range of tilt in either direction. Even a range of 60 degrees tilt in either direction would overcome the great majority of spinal curves. It would also be of great advantage to have the overcouch tube capable of being fixed lateral to the table and moving with it, to provide dual plane screening and radiography without the necessity of constant stoppages for positioning.

Clinical problems.—Myelography may be indicated for three reasons:

(1) To localize a lesion where the clinical level is doubtful.

(2) To show or exclude multiple lesions, perhaps either neoplasms or protruded discs. Except where the clinical signs cannot be correlated with changes on straight radiography I do not believe that myelography is either necessary or desirable as a routine in lumbar disc protrusion.

(3) To afford evidence as to the extent of a space-occupying lesion and as to whether it is likely to prove intra- or extra-medullary at operation.

The most difficult problem in myelography is the correct assessment of partial defects, especially when the contrast medium has become fragmented into droplets. In any such case screening should be carried out both prone and supine, and repeated in the suspected area. I must stress again that an adequate quantity of contrast medium is essential, and in any case of doubt I would not hesitate to inject a further quantity even if it meant withdrawing some later.

Difficulty can sometimes occur if the contrast medium is partly injected or leaks into the epidural space. It is important to recognize this occurrence and inject further material into the subarachnoid space if possible.

In all cases the examination should be carried from the sacral to the cervical region, even in those cases where lumbar symptoms only present. It seems likely that too little attention has been paid in the past to the possibility of a lesion in the upper part of the cord causing signs at a lower level, and that failure to carry out a complete examination may have led to such a lesion or multiple lesions being overlooked.

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Dr. R. G. Reid (Department of Radiology, Manchester Royal Infirmary) and **Mr. G. K. Tutton** (Lecturer in Neurosurgery, University of Manchester):

Dr. R. G. Reid: The aim of the radiologist when, with contrast media, he seeks signs of a space-occupying lesion in the hollow structures, is not merely to disclose the presence of a lesion, but to try to determine its precise position, its size and shape and its pathology, and having done so to be on the look out for other lesions since they may be multiple. This information he strives to obtain from the characteristics of a filling defect in the contrast medium.

In myelography, the hollow structure is a tube formed by the dura mater with its inner lining of closely adherent arachnoid. But the cavity, the subarachnoid space, is not, as it were, a void as is that of the alimentary tract, the ventricular system and the bronchial tree; for passing through the greater part of its length is the spinal cord, closely invested by pia mater, forming a central core, which therefore converts the space into a shallow water jacket.

This cavity is further occupied and complicated by paired anterior and posterior nerve-roots, extending outwards from the lateral aspect of the cord, and which, on passing through the arachnoid and dura, carry with them for a short distance a loose collar of these membranes which form pockets, root pockets—into which the contrast medium may flow. Still more space is taken up by the suspensory ligaments connecting the pia and arachnoid and alternating with the nerve roots up and down the cord (Fig. 8).

The space, then, is complex and offers ample opportunities for disturbances in free flow of contrast medium through it. That is why a filling defect must be constant to be of significance. Its radiological investigation is made more difficult when relatively small amounts of contrast medium are used because then only a few segments may be outlined at any particular moment. Then there are the bends in the spine producing watersheds over which it is tricky to coax the Myodil without its breaking up into droplets. This is accentuated when the normal curvature is complicated by deformity. In such cases I examine the patient beforehand to determine in which position the contrast medium will accumulate at the suspected site of the lesion.

The vast majority of spinal tumours, with the exception of chordomas and metastases, do not infiltrate the surrounding bone and are benign. Unlike some intracranial tumours, they do not produce a generalized reaction on the bone, yet they often cause changes in the surrounding osseous structures, due to pressure. At first the bone becomes decalcified, and if the pressure continues, the bone may become eroded and destroyed. In their earlier stages these effects may easily be overlooked in the generalized routine radiological examinations of the

spine. It is only when, by myelography, attention is directed to a certain region that subsequent careful X-ray investigation—coned views in several projections—will reveal them.

Such bony changes may yield more exact evidence of size and site and sometimes of the nature of the lesion than will myelography. It is only by reference to the degree of bone erosion that the size of the tumour can be assessed. It may obviate the necessity of introducing myodil both cisternally and lumbarly to determine the upper and lower limits of the tumour. Therefore, by correlating the straight and the myelographic evidence we get a more accurate radiological diagnosis (Fig. 1).

FIG. 1.—Erosion of lamina of T11 by a neurofibroma which lay extradurally but had an intradural extension as shown by the complete arrest of the myodil.

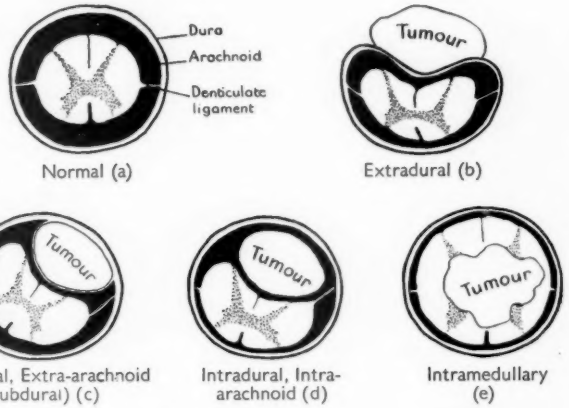


FIG. 2.—Diagrams to show the effects of tumours compressing the spinal cord on the subarachnoid space (in black). (a) Normal cord. (b) Extradural tumour. (c) and (d) The two types of intradural extramedullary tumours. (e) Intramedullary tumour.

In the general X-ray examination of the spine the earliest sign of bone erosion is usually to be found in the pedicles.

Normally oval their medial margins become flattened, later concave, and finally disappear altogether.

When the degree of erosion is but slight it is to an increase of the interpedicular distance, an indication of the width of the spinal canal, that one should look. Elsberg and Dyke compiled a chart which gives the average and extreme interpedicular distance of all the vertebræ from the 3rd cervical to the 5th lumbar inclusive. Such a chart, based on 300 normal cases, makes it possible to compare the measurements of any given case with a normal standard, and obviously may be very helpful in locating and estimating the extent of a tumour (*see* Elsberg, C. A., and Dyke, C. G., 1934, *Bull. Neurol. Inst., New York*, **3**, 359–394).

As radiologists, we should look upon spinal tumours as being classified, not from the structures in which they arise, but according to their relationship with the subarachnoid space. Terminologically it amounts to the same thing, but it is to this space and defects in it and the direction from which the defect is produced that we look for our information—we should think in terms of space. This cylindrical shallow subarachnoid space may then be encroached upon by tumours arising within its solid core, the cord, which tumours obviously must enlarge the cord so that it bulges outwards into the space. On the other hand the space may be invaded by tumours arising in its walls and projecting inwards.

The two groups are the intramedullary and extramedullary tumours respectively. Since in the latter, the extramedullary group, tumours arise in association with the inner and outer surfaces of the membranous wall they are subdivided into intradural and extradural groups respectively. Fig. 2 illustrates the effects on the subarachnoid space that are to be expected from tumours so disposed.

"Intramedullary" tumours, as they grow, expand the cord outwards into the space and form a fusiform defect within it. In practice, however, it is sometimes difficult to demonstrate myelographically into which of these groups a tumour falls; or to distinguish between the intra- and extra-dural types in the presence of a complete block.

No allowance is made in this theoretical deformity pattern for the bulk of the displaced cord, which may at times be even swollen and œdematous. Furthermore, the direction of cord displacement which influences the shape of the adjacent subarachnoid space is not straightforward (as will be explained and demonstrated by Mr. Tutton). Again, complete occlusion of the subarachnoid space is commonly found when either the upper or lower margin of the tumour—depending on whether the contrast has been introduced into the cistern or lumbar region—has produced a filling defect and, if time is allowed, the contrast medium may seep round and outline what initially seemed a shapeless barrier (Fig. 15).

The intramedullary tumour is the most readily recognizable. In the absence of complete obstruction, the outward swelling of the cord produces a fusiform filling defect in the contrast medium greatest at the mid-portion of the tumour and fading off at its point of mergence with the normal cord. If obstruction is complete, a symmetrical concave filling defect in the contrast shadow will reveal it (Fig. 3).

FIG. 3.

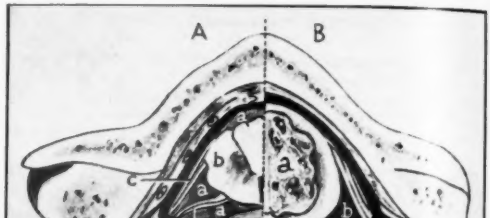


FIG. 4.

FIG. 3.—Myelogram of an intramedullary tumour. Note the extreme widening of the bony canal with interpedicular thinning and the long sausage-shaped outline of the cord with the enlarged root pockets.

FIG. 4.—Transverse hemisection of cord to show root pockets (Peiper) in a normal spine and in a case of intramedullary tumour. In A, one can see a normal half of the cord showing the relation of the cerebrospinal fluid, a, around the cord, b, and the spinal roots, c. In B, the appearance is that found in an intramedullary tumour, shown at a. In such an instance, the root pockets, at b, form the only open space and the only channel by which the opaque solution may travel down the cord. (From Pancoast, Pendergrass and Schaeffer: The Head and Neck in Roentgen Diagnosis. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

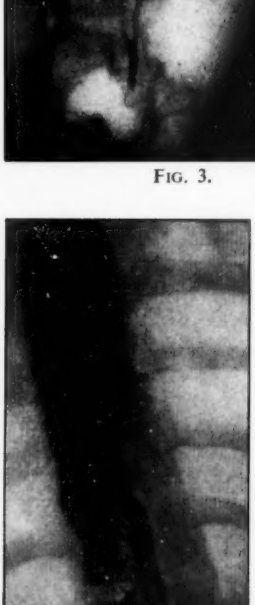


FIG. 5.—Myelogram of hæmangioma or angiomatous malformation of thoracic cord. The characteristic indentation of the myodil shadow by the enlarged serpiginous vessels is clearly seen.

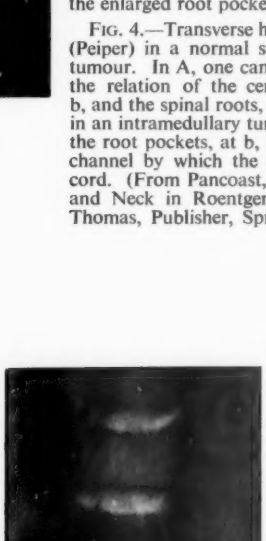


FIG. 6.—Anteroposterior myelogram in a case of anterior disc prolapse. Note the cord shifted to the right and the 6th cervical root crossing the upper part of the widened subarachnoid space on the left side. *See* Fig. 18.

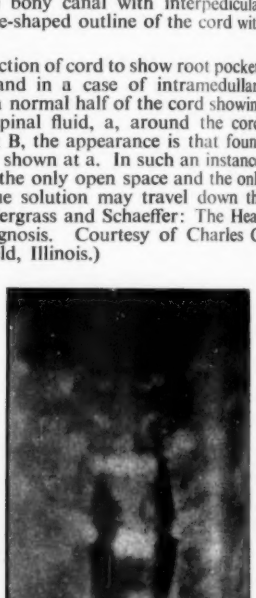


FIG. 7.—A.P. myelogram in a case of calcified median bar at C5/6 level. Note the shadows of the lower cervical roots and the root pockets.

This group forms some 20% of all intraspinal neoplasms, which are histologically similar to the gliomas of the brain. The commonest is the ependymoma arising from the lining of the central canal. It is a slow-growing type, often symptomless until of large size, and causes bone changes in a high percentage of cases. Other gliomatous types attain a large size without causing bone erosion—perhaps because they are more rapid in growth. The commonest non-gliomatous intramedullary tumours are syringomyelic cavities. Another common and essentially intramedullary lesion is the angiomatous malformation which produces a characteristic myelographic appearance (Fig. 5).

Apart from the contour assumed by the contrast medium, Peiper describes a sign helpful in distinguishing the extra- from the intra-medullary tumours: it consists in alterations in the normal pattern of the root pockets, which extend towards the points of exit of the spinal nerves. He aptly likens them to the thorns of a rose bush (Fig. 4). Small in the cervical region, they gradually increase in size caudally but normally they fill with contrast medium only well at two levels, the cervical and the lumbar.

The swelling of the cord by an intramedullary tumour, while gradually occluding the subarachnoid space, separates and widens the space between the anterior and posterior nerve roots, opening out the root pockets, into which the contrast medium flows, so that they appear larger than normal. Extramedullary tumours, on the other hand, obliterate the root pockets.

Of extramedullary tumours, the intradural in position, when non-obstructing and so completely surrounded by contrast medium, show as a sharply defined filling defect, but it is exceptional to catch them at this stage. Commonly obstruction is virtually complete, when the margin of the tumour only will show as a "crescentic" defect against the contrast medium. The problem now facing the radiologist is in determining the site of attachment of the tumour—be it anteriorly, posteriorly or laterally disposed. We think that this may be answered if and when a filling defect in the contrast medium by the displaced cord is seen. Intradural extramedullary tumours form approximately 60% of all spinal neoplasms. As a whole, they frequently cause local bone erosion, but certain types are more prone than others to do so.

The commonest types are the meningioma and the neurofibroma; and whereas the former, the meningioma, tends to confine itself to the thoracic region and cause minimal bone changes, the neurofibroma is not at all "choosey" and is the one which most often "gives itself away" in the straight radiograph. And not merely because of its destructive effects on bone, but because it may extend into and distort the normal paravertebral soft tissue shadow.

Extradural tumours, forming the remaining approximately 20% of intraspinal neoplasms, are likely to be disclosed because of their effects on the paravertebral soft tissues added to their erosive action on the adjacent bone. The commonest are the meningioma, neurofibroma and secondary carcinoma, similar in reaction to their intradural counterparts, and which, because of their position, have the opportunity of attacking the heads of the ribs. Others are the hæmangioma producing the characteristically striated vertebræ and the chondroma, arising from the margin of the intervertebral disc; and, of course, the ubiquitous retropulsed disc which is an extramedullary intraspinal tumour.

For the lumbar disc lesions we do not often use myelography but we do so for the cervical. The latter seem to be difficult problems for the neurosurgeon and I feel that something is wrong when one considers that in a third of those operated on, no disc was found. The myelograms in all suggested a partial block. We are at present working on the problem of the technique of cervical myelography and I think that we need some method whereby the myodil can be kept in the cervical region, overlying the disc spaces so that indentations can be more carefully observed.

The technique of watching the stream of myodil, introduced cisternally, with the patient sitting up in front of the screen, traversing the neck, does not seem to give sufficient time for small irregularities to be properly observed.

The following myelograms are from two cases of suspected cervical discs. In the first there was a partial hold up of the myodil at C5/6 level. Operation disclosed an anterolateral disc which will be referred to again (Fig. 18).

In the anteroposterior projection the cord shadow is well seen (Fig. 6). It is pushed slightly to the left side. The 6th cervical root can be seen as a shadow crossing the subarachnoid space. In the lateral, with the myodil spread out along the cervical canal, there was surprisingly little deformity but the column was certainly widened underneath the 5th cervical lamina.

The next case (Fig. 7) is the anteroposterior myelogram in a man who at operation had no demonstrable disc protrusion. The surgeon thought that he had a calcified median bar similar to that depicted in Fig. 19.

At the C5/6 level the myodil appeared to flow round something and the myelogram shows an area over the disc space to be devoid of contrast medium.

In some of the other cases which operation proved to have disc protrusions, a definite indentation in the lateral views of the affected disc space was seen. In none was there a complete hold up of the myodil.

A method whereby the myodil can be made to pool in this region so that good lateral radiography in particular can be taken would seem to be required if myelography for cervical disc lesions is to be more reliable.

Mr. G. K. Tutton: From the surgeon's standpoint, myelography helps to establish the existence of a tumour and its exact site.

The spinal cord is enclosed in dense bone, and therefore the operation on a spinal tumour must be at precisely the right level, and with a limited and direct approach. The surgeon is helped, therefore, if radiography can pinpoint the tumour in relation to bone structures. Further it is possible to operate in quite the wrong place or even to miss a small tumour if clinical facts alone are relied on.

In our experience, myelography with either myodil or pantopaque has never failed to disclose a tumour, if present. I believe that missed cases are usually due to inadequate technique.

Myelography is not suitable for all cases. Some patients are not fit enough for it, whilst in others plain X-rays, when viewed in the light of the clinical findings, will give a precise localization (Fig. 1).

Some myelograms have been performed in order to obtain a pictorial record, and also better X-rays of the actual site of the lesion (because the radiologist can cone down at the site of the block).

The following analysis of 105 consecutive cases of spinal lesions (all known to me personally from Sir Geoffrey Jefferson's Neuro-surgical Service in Manchester over the last two and a half years) shows that myelograms were done in 60% of the total cases, in 80% of tumours, in *all* the cervical discs, but in only 15% of lumbar disc cases. We have not used myelography extensively in these last because our decision to operate has been based more on clinical signs and symptoms.

Acute extradural spinal abscesses should never be subjected to myelography—and indeed it should never be necessary in these urgent cases. Chronic extradural granulomata, of which there were none in this series, will usually require myelography.

The number of tumour suspects is small because the neurosurgeon never sees many cases primarily investigated by the physicians and—because of negative myelographic findings—never referred.

With the exception of one case of unsatisfactory air myelography, which failed to demonstrate a tumour two years ago and is now included in Table I, no tumours in this series were missed by myelography.

TABLE I.—MATERIAL: 105 CASES OF SPINAL LESIONS

	Total numbers	Myelograms
Spinal Tumours:		
Extradural	13	7
Intradural		
(*a*) Extramedullary	20	18
(*b*) Intramedullary	9	8
Disc Lesions:		
Cervical	14	14
Dorsal	1	1
Lumbar	33	5
Adhesive arachnoiditis	1	1
Extradural spinal abscess	4	0
Transverse "myelitis"	1	1
Myelopathy (cause unknown)	4	3
Suspected spinal tumour	5	5
	105	63

Air myelography.—We have in the past two and a half years used this method on some half a dozen occasions, but not with great success. It is potentially of great value provided that an indeterminate result does not deter one from using another contrast medium. It should be a valuable method of showing up the cord and its shift above and below a lesion.

If we look more closely at these figures it is striking that only half of the extradural tumours had myelograms, due, I think, to the frequent presence of obvious bone or soft tissue findings on plain X-ray films. The high proportion of myelograms in intradural but extramedullary cases indicates that changes on plain X-rays are often minimal. 12 of these tumours were dorsal, 5 were cervical and 3 lumbar. Tumours in the last two sites are often impossible to localize exactly without myelography.

The case of myelitis and two of the myelopathies were explored because of partial "hold-ups" but none of the tumour suspects.

Of the remaining nine tumours which did not have myelograms, six had clear changes on the straight X-ray films, such as dumb-bell tumour in the mediastinum (1), pedicular widening (2), bone destruction (2), or ossification in the tumour (1), findings which fitted exactly the neurological level.

The seventh was a neurofibroma anterior to C1, and the patient was so breathless from impaired respiratory muscle function that we had a Drinker's respirator waiting in the ward. A high cervical situation was obvious although, of course, its pathology was not. We thought it might be intramedullary. Even moving this man to the X-ray Department was, we considered, fraught with danger but in the end all went well.

In the remaining two myelography would have helped—the first, an old man of 71 with a few months' history, had one of those soft neurofibromas at T1 which was at least 2 segments above the neurological level. We wasted half an hour unnecessarily exploring below the site and he nearly died of shock but he too is well today. A myelogram had been considered superfluous.

The last case was one of intradural neurofibromata (Recklinghausen) with numerous tumours on the skin, and café-au-lait marks. We were confident that the clinical signs indicated lumbar 1/2 level, but the tumour causing the trouble was at cervical 5! Myelography came to our rescue for the second operation.

30 myelograms were done by the cisternal and 33 by the lumbar route. Liaison is essential at all stages between radiologist and clinician.

Broadly speaking we use the cisternal route for all cervical or upper dorsal cases and the lumbar route for the lesions below about T6. Certainly the cisternal route is the best for the cervical discs. Often, too, in thoracic tumours when all we want is a level which can be exactly marked on the skin and the procedure means only that the patient be sat up or supported in front of the screen for five minutes the cisternal is the route of choice.

The tilting table technique is, for the ill and paraplegic, a trying experience and should be avoided. Note that paraplegic tumour cases nearly always have sensory levels. The great value of the tilting table method is, in my opinion, in the early case with slight signs, or to differentiate degenerative and other non-space-occupying lesions.

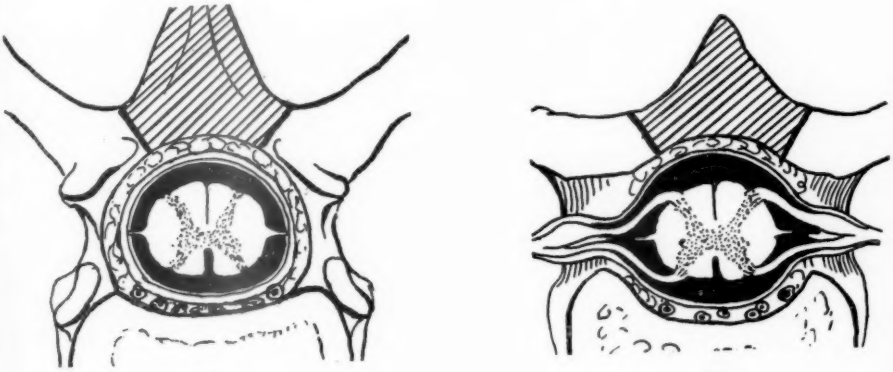
If a tumour is clinically present, what then is the value of myelography? It is first and foremost to establish the exact level so that our incision may be as small as possible and secondarily—very secondarily—we hope it will tell us (a) in what relation the tumour lies to the cord, i.e. extra-, intra-dural or intramedullary and (b) whether it lies in front, behind or at the side of the cord or in a combination of these positions.

This is the data which the operator wants and so rarely gets. If the block is complete we can usually tell only location with certainty. If the block is incomplete then some of the other data may be forthcoming. In this series 26 of the 33 tumours had complete arrests and it was impossible before operation to be dogmatic about anything other than the exact site. Two of the intramedullary cases could, however, be diagnosed with certainty, but two could not—one indeed looked like a typical extradural tumour and two more would have done for intradural but extramedullary. In only two of the whole bunch of thirty-three tumours was the obstruction sufficiently incomplete to allow of reasonable conjecture between an intra- or extra-dural site.

These results refer only to this series of cases—I have seen several cases of incomplete blocks with neat filling defects, which usually only happen with small intradural extramedullary lesions, but they are much less common than is supposed. Perhaps we get our cases very late—owing to our long waiting list.

The Subarachnoid Space

The subarachnoid space is the key to the situation—because myelography is really the visualization of this normally capacious space. The suspension of the cord in the cerebrospinal fluid is lateral by the nerve roots and ligamenta denticulata—thus allowing anteroposterior movement but little side-to-side movement (Fig. 8). There is, too, less space in the cervical and lumbar enlargements. When a tumour is present in the spinal canal the space is first narrowed locally and the cord gently pushed away and dented. Signs are minimal at this stage.



(a) (b)

FIG. 8.—Two transverse views of the cord and its covering to show normal relationships and in particular subarachnoid space (in black). In (b) the section is at the level of the emergence of the nerve roots whilst in (a) it is midway between this point. The shaded areas represent usual bone removed at operation.

In Fig. 2 you will see a normal cord and early extra- and intra-dural and intramedullary tumours. The subarachnoid space is in black.

The intradural extramedullary tumours are, I believe, primarily (a) extra-arachnoid and (b) intra-arachnoid. A distinction of value when considering the effects on the subarachnoid space (Fig. 2).

As a tumour enlarges, the cerebrospinal fluid cushions around the cord are gradually obliterated. In an extradural tumour this process is very slow and may never be complete (Fig. 9), accounting probably for the very long histories sometimes encountered in these cases and the tapering ends of the myelographic shadow. In the intradural tumours, particularly those arising within the arachnoid, pressure on the cord is exerted earlier since the protective cushions of cerebrospinal fluid are obliterated sooner. Even more important perhaps is the site of the tumour. If completely anterior or posterior the cord can move away more easily and signs are less marked, hence the histories are often long. When lateral either in front of or behind the dentate ligament, histories tend to be short and signs very obvious. Thus a tumour may arise either anteriorly or posteriorly and remain so for many months or years. If a lateral extension occurs then signs and symptoms rapidly become more manifest. This fact explains the long histories with sudden deterioration, in cases of meningioma particularly.

Put another way, purely anterior and posterior lesions are better tolerated by the cord than lateral ones, hence signs are maximal in lateral lesions or where lateral extension has taken place. Thus, when assessing the significance of length of history with the myelogram, the retention of the cerebrospinal fluid cushions is one part of the story—and the lateral fixation of the cord the other.

In practice the common myelogram finding is a block.—Just that—occasionally some medium will get by if the posture is changed. The deflection of the cord can usually be seen adjacent to the block—the cord outline appearing as an area of diminished opacity in the myodil (Fig. 12).

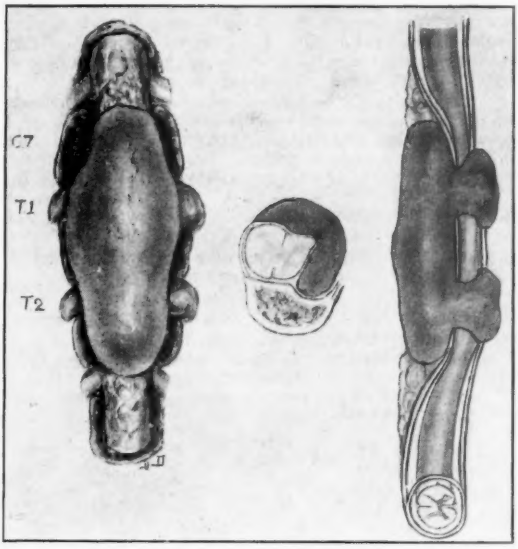


FIG. 9.—The tumour has flattened the spinal cord but not completely obliterated the subarachnoid space. Note, too, the tapering of the space above and below the lesion, and the hypertrophy of the extradural fat. The gradual tapering of the space accounts for the gradual thinning and irregularity of the myodil shadows in these cases as the site of the lesion is approached from either above or below.

It should theoretically always be possible to detect deflection of the cord. I would think that air myelography could be of the greatest value in this regard. In general the complete blocks, owing to the vagaries of arachnoidal adhesions, tell us little apart from the exact location, but the following case illustrates additional information which can sometimes be obtained.

Female, aged 58. Twelve months' history of girdle pain around abdomen and progressive weakness of the legs. On examination there was a clear sensory level at segment T9, with increased tone in the legs and weakness of all muscle groups. Lumbar puncture showed a complete block on jugular compression. Protein 180 mg.%. Straight X-ray of the spine showed no abnormality.

Myelography was performed by the cisternal route with 3 c.c. of myodil (Fig. 10). A complete block was present at D7 level. The tumour, a soft neurofibroma, was completely removed (Fig. 11), the patient making a complete recovery. In Fig. 12 a correlation between the myelographic findings and what was found at operation is attempted—the wider "limb" indicates the side of the tumour and the narrower the side of the cord.

The conclusions we might draw are that in a complete block the wider subarachnoid space above the site of the block is on the same side as the tumour. At the level of the block any prolongation of the subarachnoid space is probably on the side of the cord opposite to the tumour and represents the remains of the protective cerebrospinal fluid cushion.

The difficulties of interpretation of A.P. and lateral myelograms are in part due to the three-dimensional changes which cannot be clearly shown by two-dimensional views.

Neat filling defects on myelography are seen only in early cases of tumour compression. Neurofibromata of meningiomas intimately attached to a posterior nerve root and hence producing pain are most likely to give this appearance since they present early.

It may be of interest to show some typical myelograms and then what the lesion looked like at operation.

First an extradural tumour (Fig. 13): The myelogram indicated a complete block and gave lower pole only. The tumour, a chondroma, had at least an eight-year history. It lay mostly anterior, and I think the lateral extension was responsible for the sudden recent deterioration which brought him under our care.

Next an intradural extramedullary neurofibroma in the cervical region, history eleven months—diagnosed as "brachial neuritis and hysteria". Over the last two months weakness of legs and sensory impairment.

The myelogram (Fig. 14A) (3 c.c. myodil from below) shows an irregular block, which seems oddly at variance with the operation photograph (Fig. 14B). Note the tumour lifting and deflecting the cord. Although arising from a posterior nerve root it lay in front of the attenuated dentate ligament.

The following myelogram (Fig. 15) would seem to give all the information the surgeon could want. Precise localization and a nice round upper border of tumour. At operation to our chagrin all that could be seen was a segment of swollen cord. After a long search which included needling the cord, a completely anterior neurofibroma (dotted lines) was found below the swelling after removal of another lamina (Fig. 16). Cord swelling above a tumour is rare. The myelographic block was produced by it in this case, a rare pitfall. The history was of three years and the signs some weakness and stiffness of the legs, facts in keeping with its completely anterior situation.

Another important aspect of myelography is its value when two lesions are present.

The following case gave rise to difficulty because the plain X-rays showed Paget's disease of the lumbar spine. The symptoms of weakness of the legs and lumbar II and III root involvement seemed to fit in with this diagnosis. A year later when first seen in this clinic myelography revealed complete block at T12 and the tumour —a neurofibroma—was removed. [Illustrations shown at the Meeting are not reproduced owing to lack of space.]

Cervical Disc Lesions

14 cases were explored. In 9 only was a convincing lesion present. Yet all had positive myelograms with either an incomplete arrest or a filling defect on screening, i.e. the myodil could be seen running round or over an obstruction.

Our indications for operation are cord compression with pain and root signs in the arms—but never on this score alone—and a positive myelogram. A negative myelogram we consider indicates a degenerative lesion—the common differential diagnosis. All the positive cases in our series have had changes on the straight X-rays, such as joint space narrowing and osteoarthritic lipping. In contrast to lumbar discs (and this applies to the rare thoracic discs too) they are the most difficult operations technically we have to deal with in the spine. A lot of bone has to be removed—a combined intra- and extra-dural approach used and, most important, no

Left Right

FIG. 10A.

FIG. 10B.

FIG. 10.—Thoracic intradural neurofibroma. (A) A.P. and (B) lateral myelograms. On the former there is an appearance of two limbs, with the left limb wider than the right. Between the two there are several blobs of myodil which do not appear as dense. Note also that some of the myodil has passed below the obstruction. The widest limb represents the subarachnoid space around the cord which is displaced to the left just above the upper part of the tumour. The greater depth of the subarachnoid space from before backwards produces a greater density of myodil than in that part of the space directly overlying the cord (*see* inset, diagram, Fig. 12). In the lateral myelogram the outline of the cord can be seen as an area of decreased density at the upper end of the myodil shadow. Lower down it fades but there is a narrow tongue of myodil on the anterior aspect which indicates that the tumour is predominantly posterior in situation since it is completely occluding the subarachnoid space posteriorly. The anterior cerebrospinal "cushion" is left intact longer.

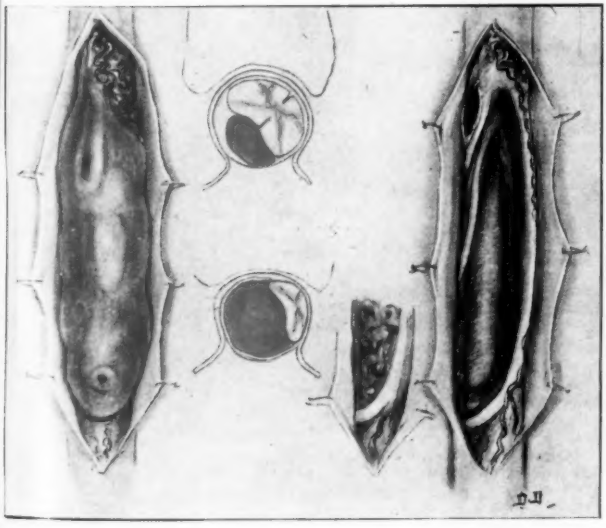


FIG. 11.—Same case as Fig. 10. At operation. The drawing on the left shows the state of affairs after opening the dura. Note that the tumour is predominantly postero-lateral; that on the right shows the extreme flattening and deflection of the cord to the left. Note the greatly elongated nerve roots. The ligamenta denticulata were doubtless destroyed by the tumour as it enlarged. The inset drawings indicate transverse sections at the upper pole, middle of the tumour and lower pole respectively.

retraction of the cord is permissible. One has to burrow laterally and underneath the cord. Paraplegia can be produced, as a result of cord retraction, and even death. These lesions are devastating in their effects and they are small. These two facts account for the negative explorations. If the lesions are completely anterior and ossified into a bar, they are most difficult to get at and almost impossible to remove.

These cervical discs fall, in our experience, into three groups.

(1) The anterolateral protrusions which cause pressure on the cord and also "pin" a nerve root prior to its exit from the intravertebral foramen (Fig. 17).

(2) Diffuse bulge without much root involvement—these lesions are more medially placed (Fig. 18).

(3) The ossified types which may be a median bar or part of a bony ridge rising from the attachment of the annulus to the backs of the vertebral bodies (Fig. 19).

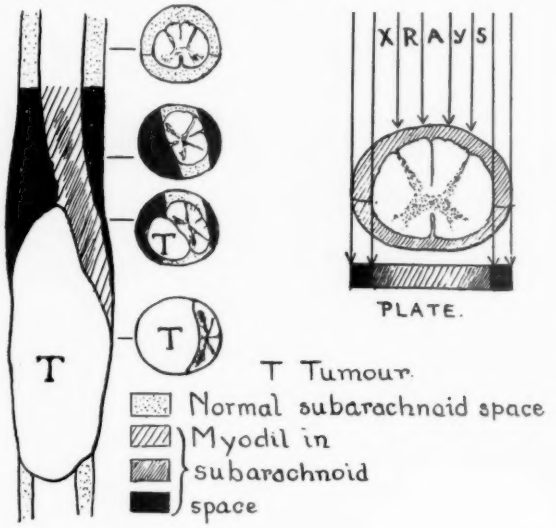


FIG. 13A.

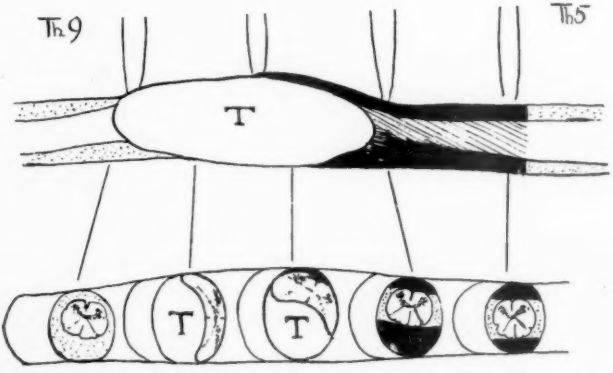


FIG. 12.—Same case as Fig. 10. Diagrammatic correlation of Figs. 10 and 11. An attempt to show the changes in the subarachnoid space diagrammatically by correlating the myelograms at various levels in both A.P. and lateral projections. They are intended to show how the cord is deflected, changes which are depicted in the small sections of the cord. The inset diagram illustrates the principle of varying density caused by the depth of the subarachnoid space so that the cord will always appear as a central less dense shadow surrounded by a denser zone.

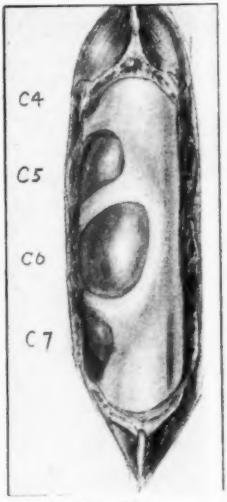


FIG. 13B.

FIG. 13.—Cervical extradural tumour—chondroma. A, myelogram—3 c.c. myodil from below because cisternal route failed. Note the complete block with cord outline displaced to the right. The greater density below the block gives, therefore, the side of the tumour. B, sketch of tumour at operation. The myelogram block would be at lower pole marked C7 on drawing.

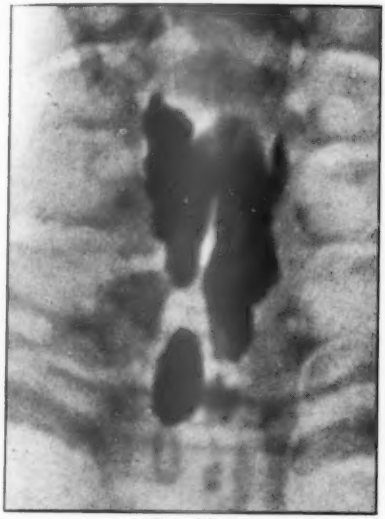


FIG. 14A.

FIG. 14B.

FIG. 14.—Cervical intradural neurofibroma. A, myelogram by lumbar route complete block at C5 level with irregular outline. B, tumour at operation after opening dura. Note the deflection of the cord and the large subarachnoid space above the tumour. The irregular shadow at the level of the block in the myelogram was due to adhesions in the subarachnoid space.

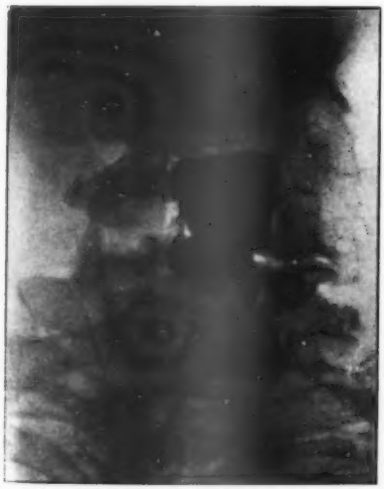


FIG. 15. — Cervical intradural neuro- broma. Myelogram by cisternal route aken after one hour, showing seepage of iyodil round the obstruction.

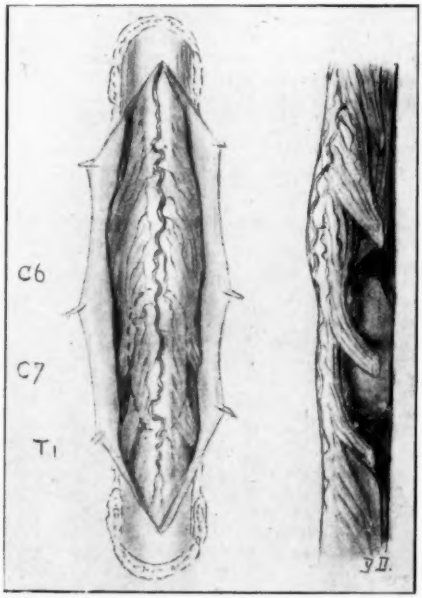


FIG. 16.—Operation sketch of tumour. Note the swelling of the cord above the site of the tumour, which lies completely anterior to the cord and is indicated by the dotted lines.

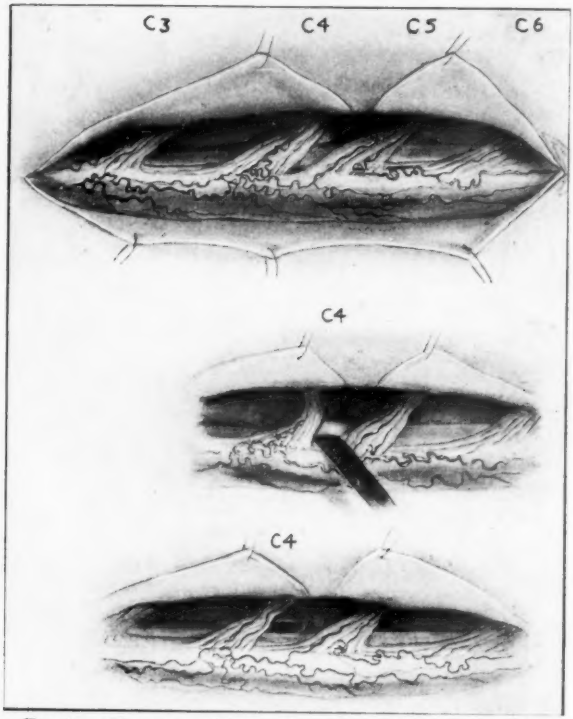


FIG. 17.—Three operation drawings of an anterolateral prolapsed cervical disc. The myelogram showed a lateral defect at level C4/5 and a partial block. In the top drawing C4 root is held tightly by the disc; the next picture shows it more clearly. Note, too, the backward bulge of the cord. In the bottom picture the hole into the joint space after removal is seen and the nerve root is now quite slack. Pressure atrophy of the lateral part of the cord between C4 and C5 was very noticeable after the removal of the disc.

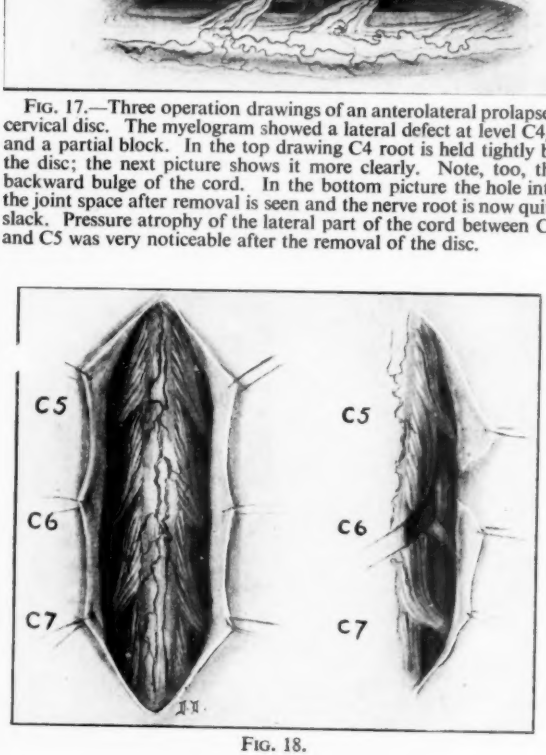


FIG. 18.

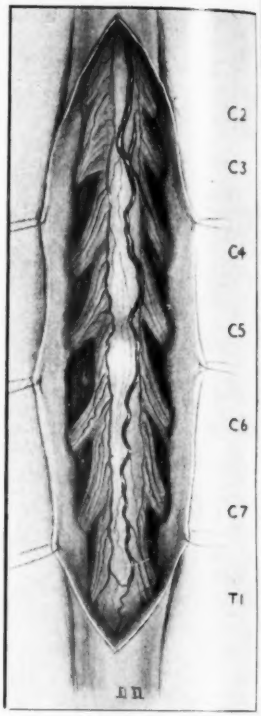


FIG. 19A.

FIG. 19B.

FIG. 19.—A, operation sketch of calcified disc. B illustrates our conception of its relation to the vertebral bodies.

At the C5/6 level the cord is obviously humped backwards and looks paler than the rest. On the left side at this level, between the roots the bony bulge is apparent. Removal of such a lesion is virtually impossible.

FIG. 18.—Operation sketch of cervical cord in a completely anteriorly situated disc. The myelogram is seen in Fig. 6. The cord opposite C6 arched gently backwards and looks paler than the rest. In the smaller picture a diffuse bulge above the roots of C6 is seen.

We have not seen enough myelograms of these types to make dogmatic statement about typical appearances. In none, however, has the block been complete. The anterolateral ones have given the appearance of a lateral indentation round which the myodil has flowed or the effect of a "bite" out of the column.

The second and third groups have produced partial blocks with, in the lateral pictures, definite indentations of the myodil column over the joint space. In the A.P. views the effect of a narrow shelf has been observed several times. This latter appearance was seen in the negative explorations too. We are of the opinion that myelography in these cervical disc lesions is often difficult of interpretation.

In conclusion, I would wish to stress the great importance of a close liaison between the neuro-surgeon and the radiologist which is necessary in this work. Both should be present at the myelogram. Without it mistakes are apt to occur and especially is this so when the block is an incomplete one. Myelography in careful hands and interpreted with a full knowledge of the clinical findings is an indispensable aid in the management of the great majority of compressive spinal lesions.

I am indebted to Miss Dorothy Davison, medical artist to the University of Manchester, for the operation sketches.

Dr. T. Richard Riley: In his series of cases of angiomatous malformations had Dr. Reid, on fluoroscopic examination, noticed any visible pulsation of the column of iodized oil contrast medium in the vicinity of these tumours. Furthermore, in what regions of the spinal canal did Dr. Reid consider one could accept pulsation of the column of contrast medium as a normal finding?

Dr. David Sutton asked a question on the technique used at Dr. Reid's clinic in the diagnosis of cervical discs. He expressed surprise at the number of negative explorations and wondered whether the myelographic technique of examination in all these cases had been adequate and had included lateral as well as A.P. films.

Dr. C. John Hodson: Has any work been done to investigate the effect of cerebrospinal fluid on the opaque media used? The question is asked because of the recently discovered effect on barium suspension of changes in the content of the bowel.

It seemed to me that changes, particularly in the protein content of cerebrospinal fluid, might affect the behaviour of the opaque medium, especially as regards the matter of globulation.

Mr. D. W. C. Northfield said that he was glad to learn that Dr. Davies recommended the employment of adequate amounts of opaque medium; this was particularly necessary in lesions causing partial or no spinal block, and showing as a lateral filling defect; and which occurred most frequently in the cervical and lumbar regions. He thought that the medium should be introduced by cisternal puncture for all cervical and upper dorsal lesions. The most convenient method of cisternal puncture for cervical examination depended upon the careful placement of the patient, in the prone position, with the forehead resting on a small pillow of such a size as to maintain a slight though definite degree of cervical lordosis. Puncture in this position seemed safer than with the patient erect, as the patient could not jerk the head forwards. As the medium was injected it flowed into the concavity of the cervical spine—provided care had been taken with the position of the patient and the general tilt of the table. Inaccurate positioning would allow the medium to escape immediately into the cranial cavity or the thoracic spine.

Dr. Ingmar Wickbom: We still prefer oxygen as contrast medium at the Serafimer Hospital in Stockholm.

Even if pantopaque and similar substances are less irritating than lipiodol, I still think that, at least in some cases, they may cause adhesions if they are not removed. This is proved by the fact that after some time the contrast is more or less fixed. This is even more clearly shown if an air study is performed. Those parts of the subarachnoidal space where some drops of oil are left can often not be adequately filled with oxygen, and sometimes even a more or less complete occlusion may be found at the level of the residual contrast.

Another disadvantage with a positive contrast medium is that, unless several spot films are taken, one has to rely very much on the results of the screening. Using oxygen or air the whole of the spinal cord and subarachnoidal space is visible on five or six films.

Mr. Tutton said that he gave up air as he had missed one tumour. This is of course the most important question, whether you can trust your method or not. We have used the method for more than ten years, having done between 100 and 200 examinations every year. To my knowledge we have not missed a tumour; as the follow-up system at Professor Olivecrona's neurosurgical clinic is very careful, I think that this can be considered a fairly reliable statement. A proper technique is absolutely necessary; a good quality film is more important than if positive contrast medium is used.

Dr. M. H. Jupe felt that because certain disc protrusions only appeared when the spine was fully extended this might well have a bearing on the fact that the protrusion was not apparent at operation in some cases when it had been seen during radiological examination. Mr. Northfield had demonstrated this protrusion on extension to him on several occasions during operation.

Dr. K. H. Gaskell: It was interesting to hear Dr. Hugh Davies' experience that up to 6 c.c. of pantopaque used, and not later aspirated, generally does no harm. This additional bulk of contrast medium should greatly assist in those cases where bolus fragmentation occurs. The commonest cause of this difficulty would appear to be the recent lumbar puncture tap (only too often carried out with the very best intentions just before or at the myelography puncture). Dr. Hodson spoke I think of another cause for bolus-fragmentation by precipitated thecal fluid proteins. One cannot help being struck at post-mortem examinations by the degree of precipitation found in cases having a high biochemical figure.

I do not share Dr. Reid's fears of obscuring a lesion by increasing the bolus-bulk of contrast from 3 to 6 c.c. After all the bulk spreads more up and down the theca than across it in depth and the inherent density of this medium is considerably less in use than is lipiodol.

[*May* 18, 1951]

Our Research Responsibilities

PRESIDENT'S ADDRESS [*Abbreviated*]

By RALSTON PATERSON, M.C., C.B.E., M.D., F.R.C.S., F.F.R., D.M.R.E.

Christie Hospital and Holt Radium Institute, Manchester

WHEREVER radiology is practised it needs to be linked with a greater quota of research activity, particularly in the field of clinical investigation, than at present exists.

As one of the younger branches of medicine concerned with a rapidly developing art radiology need have no fears of comparison with other branches of medicine, as far as original work is concerned. Yet even so, the sciences of both radiodiagnosis and radiotherapy are already getting somewhat stabilized and have left their early highly experimental beginnings behind them. We must now see to it that our ideas and procedures are kept constantly under review. The mechanism of such critical surveillance is research. In so far as my own field of work is radiotherapy I naturally orientate what I have to say to radiotherapeutic problems. I am very sure, however, that the same principles could be applied to radiodiagnosis.

By research is meant *planned* investigation based on a critical attitude to present conceptions of diagnosis, or treatment, and applied to determining the true scope and most effective application of new knowledge, or to arriving at measurement of causes or effects.

In the ordinary way to do research of substantial value a man must be able, and be enabled, to give at least half his time to that aspect of his activities. Moreover, by the very nature of research that contribution will be confined to cultivation of one tiny corner of his specialty. Because of this there is much to be gained from the stimulus of having some ordinary clinical work running concurrently. Nor is this stimulus only one way; the discipline of research reflects back into and illuminates his routine clinical work.

Whole-time research work is very largely for the worker on fundamental radiobiological problems where the techniques and approach necessarily differ from those of clinical radiotherapy and where both experience and aptitude may not be suited to the clinical arena. Even there, however, there are many who would gain by not being too remote from the patient, and by being given opportunity and responsibility for a quota of clinical work. Where training or aptitude makes this undesirable, the other solution is that clinical worker and research worker have ample opportunity to intermingle.

There are many types of research. In the first place there is true *laboratory research*, basic or fundamental. It is concerned with illumination of the fundamental processes on which a particular branch of medicine has been built. In our case its task is to provide us with a clearer picture of the intimate reaction between radiation and living tissue. Its domain stretches from the study of the elementary initial effect of radiation on water as the universal substrate. Then through the complexities of action on proteins, nucleic acids and other cell components. From this we reach the special problems of whole tissues and organs and lastly there are the effects on whole organisms in which the complexity of the problems become more and more baffling. *Very much more* of this pattern of research could profitably be done. But it does call for collaboration of workers in a variety of fields and for team work. It necessitates, therefore, some kind of organized unit with considerable facilities. This basic research is not only a source of inspiration but is also a rich medium for the clinical investigator. Yet we must realize that this is not the only source of research material and that much can be done in the clinical field itself. Indeed it is stimulating to reflect how our present-day practice still depends not so much on academic principles discovered in the laboratories, as on accumulated empiric knowledge acquired by the old, slow, and in some ways clumsy and inefficient methods of trial and error—plus clinical intuition.

Secondly, there is research concerned with developing the instruments or processes we employ, or concerned with improving the methods by which we apply this armamentarium. Though vitally important to therapy and, in so far as we all love playing with gadgets, vitally interesting to therapists, for the most part we, as clinicians, are not in a position to make major contributions in this field. This is the home ground for our colleague the Physicist. The key work is done by him, our own contributions being mainly support and encouragement, and occasionally taking some of the credit! The medico-biological and the medical field are ours—wide open and waiting to be cultivated by us. In this field of instrumentation and pure technique we are only learning how to do better that which we are already doing—not something new and different. For instance, in the modern trend towards increasing accuracy in small volume therapy, as in beam direction, or as in the use of higher and higher voltage for its *physical* superiority, we can overcome the limited sensitivity of some types of tumour by reducing volume irradiated safely. Yet thereby we come no nearer the more crucial problem of altering inherent radiosensitivity.

We accept that as it is and then, technically, make the best of the situation so presented. We all dream of improving results in that present-day scourge—lung cancer. With megavolt therapy we might with luck get as much as a 50% improvement. To expect more than that is pure fantasy. But what does this really mean—the present 3% to 4% at 5 years raised to some 6%, important to the 2% affected but not a spectacular advance. Innate volume of tumour when first diagnosed still defeats us. But with some method of changing radiosensitivity—drugs, time factors, sensitizers—we might make this cancer curable in larger volumes and then we would lift it into the mouth, skin, cervix class at 30%–40%—and lift these latter to spectacular figures.

So thirdly there is *clinical research, our* task and one which merits closer examination. Much more should, and could, be done with profit and in more places.

There are many ways in which investigative work can be done at clinical levels which is still true planned research and not merely inspired natural improvement of method and idea. I propose to analyse two of them.

One is individual study of patients and of treatment with a degree of completeness and exactness such that the total man-power per patient is far in excess of that ordinarily expended in purely utilitarian work. But mere amount of work and profusion of tests, examinations and analyses do not of themselves make for knowledge.

Any investigation of this kind will inevitably concern one tiny little corner of the subject, and be by its nature very narrow. So it seems to me that for the most part clinical research should be carried out on a part-time basis—the half-time previously referred to. But the research half must be kept sacred and in that half at least it should be possible to work with that feeling of leisure and unlimited time which leaves no bar to the taking of infinite pains, for ultimate success depends thereon.

This meticulous study kind of research can only pay dividends when planned to definite purpose. It is all too liable to be sterile unless the investigator has clearly formulated the question or series of questions to which he is seeking an answer and is capable of building up new concepts from the data he obtains.

Let me again illustrate by example from a field with which I am for the moment concerned, the application of radio-iodine to thyroid cancer. The broad question is, of course, can we make I^{131} cure thyroid cancer? But that question of itself is not nearly specific enough unless one is content with a "give some and see". We need a much more specific approach:

(1) What kind of tumours pick up iodine—and later "why"?

(2) Can any of the types of thyroid cancer which do not pick up iodine naturally be made to do so artificially, or can they not?

(3) The limiting factor in treatment may well be whole-body radiation. What is the limiting dose of radiation given this way and how can it be measured?

(4) How homogeneously is the radio-active iodine distributed in tumour when picked up? In other words is it even theoretically possible to kill the whole tumour with one shot?

(5) Can we devise tricks by which we can augment rate of pick-up and so save, relatively, whole-body radiation? and so we might go on.

One aspect of the detailed study type of research needs comment. In this technical and biochemical age it nearly always calls for considerable supporting laboratory study. This has nothing to do necessarily with basic laboratory research but is something quite different. Yet it does entail expenditure and man-power. Fortunately, it may often be met on relatively limited lines as one is not concerned with the whole gamut of laboratory activity but with merely one or two specific tests or processes related directly to the subject in hand. It seemed to me that in the United States they showed a greater capacity than we do to tie up small laboratory projects with their clinical investigations, often right on the spot in the ward side-rooms.

The critical question is, of course, who is going to do this kind of work? We are all up to the neck with what one might call utilitarian medicine, rising numbers of patients, inadequate staff, and registrar cuts. Yet research should not be lost sight of. Somehow or other time must be made for those with appropriate talents. The solution is, I know, one which needs making on a national basis for all medicine, but let *us* do now as much as we can with the means at our present disposal.

Then there is another type of clinical research which might prudently be well encouraged at our present stage of radiotherapeutic development and which though equally valuable is less time-consuming—the *alternative treatment experiment*. It is, at least, something not needing additional man-power and to which almost everyone could contribute something, even if it does take a few years to mature.

We are all aware how much laboratory research is based on the principle of control groups of material. It is obvious that in clinical medicine the system of controls as used in laboratories can seldom be employed in its simple form, that is with a set of untreated controls as the base line of any experiment. Yet even in clinical medicine it has been done, for example in the studies on the common cold in relation to virus immunity. In the therapy of cancer this is scarcely applicable, but

wherever two different treatments are available and it remains debatable which is the better, the homologous and equally informative experiment is open to us. Now this situation often exists in a clear-cut form in modern cancer therapy. Reams of print have been used to try and prove the superiority of one or other favoured method without any convincing result because the "samples" used whether in the same centre or different centres could never be regarded as genuinely comparable. Moreover, inevitably, emotional factors and prestige factors can and do creep in. I believe that much of this stalemate will persist unless we deliberately set out on a relatively large scale and on a research basis of accuracy to make direct and absolute comparisons. This entails carefully planned alternative treatment experiments with purely random allocation of cases to one or other alternative.

Here are a few examples to illustrate the scope of this kind of procedure.

(1) Where radium or X-ray are used together in the treatment of uterine cancer should X-ray precede or follow radium?

(2) Is radical X-ray treatment of breast cancer more effective at ten to fifteen weeks, as claimed by Baclesse, as compared to the three, four or five weeks which have long been employed?

(3) In the treatment of connective-tissue tumours Cade reaffirmed in his Presidential Address (1951, *Proc. R. Soc. Med.*, **44**, 19) his belief that pre-operative X-ray treatment is of real value. How easily susceptible to proof by alternative treatment test would this be?

(4) We have not yet arrived at any final agreement as to the relative merits of small-field beam-directed X-ray versus radium beam therapy, in spite of Dr. Constance Wood's suggestive but not essentially conclusive study.[1] It is about time we knew, instead of merely arguing from insufficient evidence.

(5) So, too, I think in the treatment of polycythæmia and the leukæmias we might usefully set out to compare the older classical methods with isotope treatment not, here, in terms of survival but by contrast of hæmoglobin response and length of remissions.

A more difficult series of contrasts to launch, because it is not easy to persuade the surgeon to the complete degree of collaboration needed, is the contrast between surgery and radiotherapy in many fields. For example, there is beam-directed therapy versus laryngectomy, and once again Wertheim's operation versus radium for uterine cancer is topical.

We have been attempting in Manchester to initiate a few such projects as much with a view to evolving suitable technique as for their intrinsic value and having the future installation of megavolt therapy to plan for. Comment here on some of the principles involved may be of interest. In the first place no experiment of this kind can be conducted on man except where the known results of both methods are such that no one concerned can have any twinges of conscience about prescribing either. This is a *sine qua non*. The sample, therefore, *must* consist only of such cases as are entirely suitable for treatment by either method. A case does not go into the experimental series unless this is so. Where for a particular case any preference or bias exists, that case can be treated according to that bias, but it is not included in the experimental series. Note that this presents no problem as *all* the cases of a particular type seen are not necessarily included. The only essential is that once a case is put into the experiment it stays in and chance alone determines which treatment it has. For example, suppose that in a post-operative radiotherapy breast series, treated versus untreated experiment, one particular surgeon insists that his cases all get treatment. Agreed, but all his cases must be lost to the series entirely. It is important, however, not to allow too many exceptions, as clearly the more we lessen the numbers in the experimental series the longer we extend the number of years the experiment must run to provide valid conclusions.

Once a decision is firmly made that a case can ethically have either of two treatments it is "registered into the experiment". The next step becomes allocation to one or other alternative treatment group by some method of purely random or chance selection. At first sight this seems simple but in reality it is a process the technique of which will repay study and trial of a variety of methods. Our own earliest experiment of this type was an attempt at assessment of the risks of squamous-cell biopsy. Then we attempted to provide a pairing of as nearly identical cases as possible. This seemed to the ordinary person entirely logical, but the statisticians say that such artificial stratification is not sound. We are now advised that the ideal is to provide purely random allocation of every case regardless of its individual characteristics. On the basis of statistical theory it is possible to say when such a contrast series is large enough to be considered as a reasonable sample. This indeed can be checked by comparing the distribution of some neutral factors such as age, stage, sex, or the like, to show that these factors have, in fact, sufficiently equalized within the random method of allocation. The method of randomization is itself of interest and worth thought to ensure that the experiment is to be free of unexpected bias. The classical tossing of a coin would do very nicely except that the therapist would clearly have to retire out of sight for the operation, that the result is open to errors of recording and also that it is æsthetically clumsy.

There are, however, alternative methods of achieving the same end. A card can be drawn from a pack of cards marked "Yes" or "No" and indiscriminately shuffled. Then the patient's name and number are immediately entered on the card.

[1] 1950, *Spec. Rep. Ser. med. Res. Counc. Lond.* No. 267.

Another method and one which I think might provide scope for ingenuity is to use some characteristic of the patient himself which varies in the ratio 1 : 1 or approximately so, and which cannot have any bearing on the result of treatment. For example we might use the date of birth—Even or Odd—or the final digit of the patient's hospital registration number.

Latterly we have worked a group of experiments on the basis of the patient's date of birth. It has the advantages that it is not open to subconscious cheating, and, being permanent, it is open to subsequent check.

I have gone into this alternative treatment story at some length because I believe that this ought to be made the basis for much of the developmental work of the next five to ten years in radiotherapy. Indeed, I am going to suggest it as the only satisfactory approach to some of our impending studies. Many centres in this country are getting, or have got, megavolt units of various types. There is going to be quite a crop of isotope variants of radium, and chemotherapy already provides alternatives to radiotherapy in the palliative fields. Particularly where expensive apparatus is concerned it is essential not only to find the scope of the new instrument but, thereafter, to measure its value objectively in absolute terms by scrupulously devised and honestly carried out alternative treatment tests. The new equipment would be matched with its appropriate technique against the best of present-day classical standard therapy.

An experiment of this kind is clearly easier to do in larger centres but, because of its very simplicity, it would also lend itself admirably to collaborative work by groups of smaller units.

In the fields of radiotherapy to which research of an essentially biological and medical type could profitably be applied, I shall select three themes by way of examples from a legion of possibilities.

The first is study of the "optimum" dose, using the word "dose" in the now accepted sense of "dose in time". Radiotherapy has made great strides in the last ten years in this country. Don't let us be too modest about taking the credit due to British radiotherapy. Yet reflection shows that what we have in the main done is to learn with something approaching accuracy what doses we were giving and then how to give accurately and homogeneously any predetermined dose. But if we examine critically the grounds on which we decide the actual dose to use in given conditions we will be surprised at the continuing empiricism of much of our current practice. Yet it is reasonable to presume that for any particular condition there is always an optimum dose which would yield the maximum chance of success and that it might often be found unexpectedly different from the one we actually employ. I believe that the criteria on which that optimum dose depends could, despite the obvious difficulties, be subject to scientific study and possibly measurement. To achieve it *we must ask ourselves the right questions* and set about analysis of this vital factor systematically, and not by depending on mere intuition. It needs to be done not only for each disease but almost for each stage of the cancers we treat. Much ingenuity is needed to collect and present relevant data in such a way that valid deductions can be drawn. But with luck we might make thereby comparable advance in the next ten years to that obtained through evolution of dosage accuracy in the last ten.

A second subject which constantly intrigues me is the still unexplained phenomenon of the nature of radiosensitivity with its relation to volume irradiated. Think how therapy would alter its complexion could someone devise a valid pre-treatment index of tumour sensitivity, not merely for the tumour species but for the particular individual tumour in question.

Another aspect of this same theme of resistance and sensitivity captures the imagination when we consider the dividends which would accrue from discovery of any means—clinically applicable—to alter relative sensitivity. Nor need this be in any big way; even a modest 5% or 10% improvement would make an enormous difference to the size of the squamous carcinoma which we could expect to cure.

Then lastly there are isotopes to be studied. Everybody is doing it, and in every broadcast on radiotherapy by the proverbial anonymous specialist we assure the public that that is our great new hope. But let us keep our own ideas on the subject clear and avoid mere indiscriminate and purely empirical use on a miscellaneous group of cancers, hoping, Micawber-like, that something will turn up.

There cannot now be the least doubt that the application of radioactive tracers will usher in for all medicine an era as important as was the discovery of the microscope to our predecessors. Radio-isotopes are research tools capable of immense exploitation but at the tracer level they must be regarded as tools, not as projects by themselves.

Along with the other branches of medicine we will use them, with the help of the chemist and the physicist. One problem is the take-up by cancer cells of labelled substances in the exploration of their abnormal physiology.

But if this be done with ingenuity we as radiotherapists may have additional reward by the discovery of a means to destroy certain cancers—by selective absorption of radio-active substances as with thyroid cancers and the leukæmias.

These are then three different examples of real medical research. The scope is almost unlimited and let us not be discouraged by the fact that these things are difficult, often disappointing, and

unfortunately never spectacular in the eyes of the public. Yet the dividends from an inspired idea, successfully explored, might be enormous in terms of increased cure rate.

One is tempted to contrast this again with the technical streamlining of our methods of therapy, including in this category the evolution of megavolt units. The very fact that they are obviously spectacular may generate a mega-mirage in our own and the public mind—a temptation to be resisted.

What matters is just how and why radiation of any kind, however delivered, acts on tumour and tumour host. That is *our* proper field of research.

Enough of radiotherapy. Radiodiagnosis should offer equal scope.

What is true in our limited sphere of radiology is equally true for all branches of medicine. Far too little research, and especially clinical research, is linked with the present-day practice of medicine in Britain:

Annual expenditure in the National Health Service: £355,000,000.

Annual total budget of Medical Research Council, including capital expenditure: £1·9 million.

Ratio just over 0·5%.

I know that there is considerable additional research being done under the N.H.S. in professorial units of teaching hospitals and in other ways but I doubt whether the sum of all such would double the M.R.C. figure. Even if we assume it does—1% is not an adequate fraction to give medical research its due place in the scheme of things.

Research is to medicine what operational research was to military planning in the last war, or to use another comparison, what modernization of plant and machinery is to present-day industry. One can hardly conceive of too much being done.

What are the main obstructions?

First there is the attitude that research is, in essence, but a frill or luxury, and not really vital to the structure of medicine. It is something, therefore, which tends to get cut first in the now chronic economy atmosphere.

The other obstruction is that research workers remain by tradition the financial Cinderellas of medicine. Yet research talent is rare and ought to be encouraged as something precious, and should command special rewards. Yet in practice great improvements would be made were it even rewarded on an equal basis with clinical medicine, not only in relation to what is offered to younger men but in terms of future prospects and of security. At present the attractions of the registrar-consultant ladder so outweigh what a research career seems to offer, that research talent is being strangled at birth by economic sanctions. And then people turn round and say "We'd like to get some research going but one cannot find any good men". It is all very short-sighted for in research, more than in any other sphere, the man is the key to success:

> "The real discoverer is rare in all classes and it must be the object of civilized communities to find him and foster his activities. Though generally the more able the investigator the less his demands on life's amenities, the scientific genius when found must not be expected to use all his time and energy fending for a living."—(MELLANBY.)

> "In view of the rarity with which the abilities requisite for a fine research worker are joined in any man, the search for such persons should be deliberate yet eager, the training facilities catholic and discriminating, and our support loyal and reverent before the opportunity to be shown new truth."—(GREGG.)

You may well ask, what has this to do with us? These changes in outlook and in custom have to start somewhere. Radiology has already acted as a pacemaker for medicine in a number of fields, for example in the development of and a respect for medical statistics, and in the encouragement of adequate centralization for appropriate specialties.

In this field, too, example may teach better than precept so I put it to you that active energetic development of our responsibilities for research is a clamant need of to-day.

Section of Experimental Medicine and Therapeutics

President—Professor R. A. McCance, M.A., M.D., F.R.C.P.Lond., F.R.S.

[*May* 8, 1951]

DISCUSSION ON EXPERIMENTAL APPROACHES TO OBESITY

Dr. G. C. Kennedy: *Experimental Hypothalamic Obesity.*

Physicians have recognized for a long time that obesity is associated in some way with the hypothalamic-pituitary complex. Fröhlich (1901) traced descriptions of gross obesity with tumours of this region in the clinical literature as early as 1840. Both he and Babinski (1900) related the obesity to diminished secretion of the pituitary. But Erdheim, in 1904, held that it was due to damage to the hypothalamus, and subsequent clinical work has done little to settle the controversy. Unfortunately, pathological processes are seldom so localized that they can be said with confidence to be entirely glandular or entirely nervous. However, in the last ten years experimental studies of hypothalamic obesity in animals have done something to simplify the position.

Ever since 1913, when Camus and Roussy showed that hypophysectomy in the dog never caused an increase in weight unless the base of the brain was damaged at the same time, there have been attempts to produce pure hypothalamic obesity experimentally. But it was not until 1939 that S. W. Ranson (Hetherington and Ranson, 1939) was able to do it regularly by making small electrolytic lesions in the brain with an electrode introduced from above, leaving the pituitary intact. Brobeck, *et al.* (1943) improved the technique, used much smaller lesions, got much more striking obesity, and showed that bilateral damage to the nuclei of the tuber cinereum was the essential lesion. In 1943, Hetherington, one of Ranson's colleagues, showed that hypophysectomy either before or after the hypothalamic operation failed to prevent the obesity, and concluded that the pituitary played no part in its production. The original work was done on the rat, but it has been confirmed in the cat, the dog and the monkey.

Although, clinically, cases of obesity where one can demonstrate organic damage to the hypothalamus are rare, I think one can learn something from the behaviour of these rats which may help towards an understanding of obesity in general. I shall restrict this description to some of the points which suggest analogies with human obesity. The animals I shall describe have been prepared by Brobeck's technique.

The obesity causes an enormous increase in weight, and a gross change in appearance compared with an unoperated control rat, but there is no effect on skeletal length, although most of the operations were carried out during a period of active growth. This in itself is strong evidence of the absence of any pituitary damage. The fat is distributed fairly uniformly through all the usual depots. By comparison the parenchymatous organs are spared—for example, in rats which have yielded over 50% of fat from the body as a whole the liver fat has been less than 10%.

The rat's hypothalamus is extremely small—only about 3 mm. across—and more than one hypothalamic centre may be involved in an experimental lesion. So obesity may be associated with diabetes insipidus, genital atrophy, somnolence, aggressive behaviour and so on after the fashion of the syndromes of clinical medicine. But these are not regular associations, and it is possible to produce fat rats in which the only detectable abnormality is the adiposity.

The immediate cause of the obesity, without any doubt, is overeating. Investigations of metabolic rate, intestinal absorption, spontaneous activity and so on have been carried out in various laboratories to see if these rats utilize their food better than normal ones, or save energy in any way, but they have all been negative. However, as soon as the animals recover from the anæsthetic after operation, it is obvious that their feeding behaviour is abnormal. They will attack and eat anything within reach while they are still confused from the anæsthetic; once fully recovered they are not so omnivorous, but under optimal conditions they will eat twice to three times as much as an unoperated rat in the first day, and may keep up this high intake for four to six weeks.

As the obesity develops, the food intake decreases, and we have found repeatedly that once the obesity is established a rat can maintain a weight of about 50% above normal indefinitely without any significant increase of food intake. As the animal gets fatter and its surface area increases, its basal metabolic rate must increase, but this appears to be balanced by some decrease in activity. However, we have never had a fat animal that ate less than its control. And at any stage if one gets the weight down by putting the animal on short rations for a time, then restores unrestricted feeding, the original high food intake returns and the rat gets fat again. I shall refer to this high food intake by Brobeck's term of hyperphagia.

Detailed analyses of operated rats have been published (Kennedy, 1950). They show that the increased weight is all accounted for as fat, and there is no change in the amount of body water, or in the dry, fat free fraction of the carcase. Our heaviest rats have weighed over 700 grammes, which is more than twice the weight attained by their controls, and some have contained as much as 65% of fat. Eventually the enormous accumulations of fat appear to be lethal. We have used young rats for operation which would normally have a further expectation of life of at least two years. They seldom survive for more than a year.

FIG. 1.—Obese rat twenty-eight weeks after operation. Trophic lesions of the skin had already developed, but the kidneys were histologically normal.

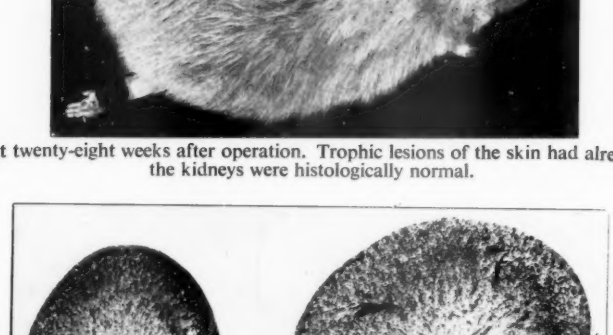


FIG. 2.—Kidney enlargement in obese rat (right) compared with kidney of litter mate control (left) sixty-three weeks after operation. Weight of obese rat 620 grammes, control 250 grammes. × 3.

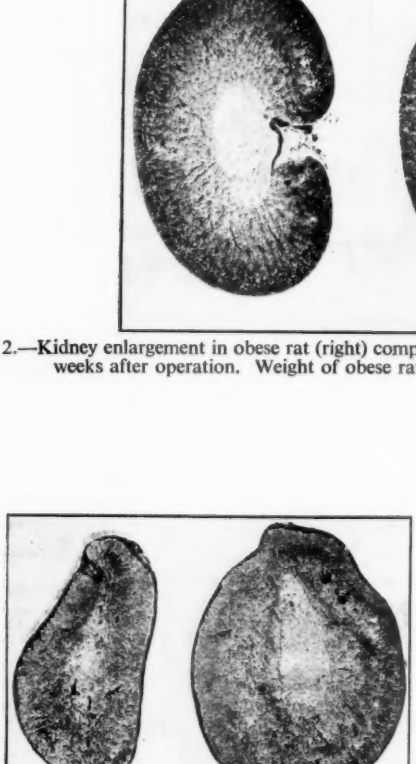


FIG. 3.—Adrenals of same two rats as in Fig. 2 × 7·5.

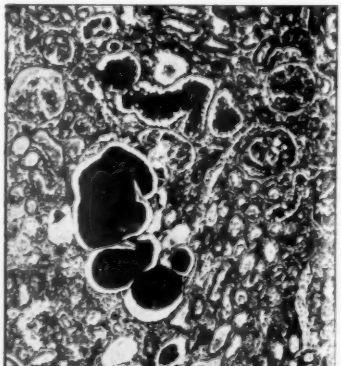


FIG. 4.—Higher power view (× 57·5) of abnormal kidney from Fig. 2. This shows a late stage of the lesion, in which the glomeruli as well as the tubules had become involved.

After six to eight months they develop trophic lesions of the skin. Fig. 1 shows a rat at this stage with large pressure sores on its feet, and a good deal of loss of hair from its back. Such animals show considerable delay in healing of wounds, even if these are placed in areas such as the back without much underlying fat, and subject to little pressure or friction.

A little later they show gross kidney damage which appears to be a major factor in limiting their survival (Fig. 2). There is severe albuminuria with rapid weight loss preceding death. The enlargement of the kidney is sometimes enormous, and is not matched by any corresponding enlargement of other organs with the exception of the adrenals (Fig. 3).

The damage to the kidney appears to fall primarily on the tubules (Fig. 4). The epithelium becomes atrophic and the lumen is full of hyaline debris. There is relatively little glomerular or vascular damage until a late stage, and although the animals are sometimes hypertensive, this is not constant. We are at present trying to elucidate the mechanism of the kidney damage. Histologically it has the appearance of pyelonephritis, which Goldblatt has shown to be common in some strains of rats. But none of our controls have shown kidney lesions, and we have found no sign of infection at any stage in the fat animals. Although it might be tempting to regard it as due to a relative deficiency of lipotrophic substances, the slight degree of liver involvement is against this. Selye (1950) has shown that histologically similar appearances can be produced in the kidney by a variety of non-specific stresses, and regards the kidney damage as secondary to over-activity of the adrenal cortex. The adrenals are certainly very much enlarged in these animals, and it is possible that obesity represents a stress in the sense in which Selye uses the term.

The feeding reactions of these animals are of some interest. The normal rat appears to be quite indifferent to changes in the palatability of its food. Mixing its stock diet with equal parts of dry kaolin powder, for example, simply results in the animal doubling the bulk it eats, so that its calorie intake is unaffected. In the early stages after operation, a fat rat will eat such a diet in even greater amount than a normal rat does, and will continue to get fat on it. But when the obesity is fully established, the rat is very much more discriminating, and will refuse to eat a kaolin mixture at all until it has used up most of its stored fat. Yet if at this stage the kaolin mixture is replaced by its normal diet, the rat will appear to be much more hungry than its control, eating twice as much as its control does. This effect does not depend in any way on the bulk imparted to the diet by the kaolin. A similar effect on food intake is produced by mild dehydration. Restriction of the water intake of a normal rat to 10 ml. a day hardly affects its food intake. Nor does it affect a hyperphagic rat soon after operation. But it causes considerable depression of food intake in fully developed obesity. This is probably only another way of reducing the palatability of food, by drying the mouth slightly. In circles where obesity still seems to be confused with œdema dehydration is often used as a treatment for the obese patient. Its success is alleged to be due to the mobilization of water. As it mobilizes fat just as well, one wonders if the treatment may be the right thing done for the wrong reason.

Pretty well any method of reducing the palatability of food, such as adding unpleasant tasting substances like quinine (Miller, Bailey and Stevenson, 1950) will affect the intake of the fat rat more than that of the normal animal. Conversely, anything which makes the diet more palatable makes the fat rat still fatter, but is without effect on its control. Sometimes merely making the diet into a wet mash instead of feeding it dry is enough to cause a considerable increase in weight.

Satiation in the rat appears to be determined then by two major factors. The intact animal always stops eating when it has got enough calories for its current needs, so it lays down no surplus fat. It is this calorimetric control which is paralysed by operation on the hypothalamus. Then another aspect of satiation becomes more important, represented in our experiments by the various conditioned reflexes affecting the weight of the obese animal. There is no fundamental difference in mechanism—the hypothalamic factor appears to be dominant in the young intact animal, the cortical one in the obese. Older unoperated rats tend to run to fat, and then they show the same reaction to changes in palatability of their diet as the operated animals do.

The basic urge to eat is never permanently reduced by hypothalamic lesions—that is one cannot produce chronic anorexia, although of course any intracranial operation may cause refusal of food for a few days. So hunger itself has probably nothing to do with the hypothalamus. The principal factors controlling food intake according to this hypothesis may be illustrated in a simple diagram.

CALORIMETRIC (Hypothalamus) ——— SATIETY ↑↓ HUNGER (Lower Centres) ——— CONDITIONED (Cortex)

This represents food intake as being controlled by a balance between hunger and satiety. Satiation has the two major aspects I have described. The release of hunger from hypothalamic inhibition causes hyperphagia. As fat accumulates in the depots a threshold is eventually reached where hunger is again inhibited and hyperphagia stops. As this stage is approached, the cortical aspect of satiation becomes relatively more important.

The nature of the stimulus to which the hypothalamus reacts is a matter of controversy. Brobeck believes it is the heat produced by the ingestion of food. We believe it to be the level of circulating metabolites, whether these are derived from ingested food or from turnover of the fat depots. We have published some of the evidence for this view and are preparing further evidence for publication (Kennedy, 1950; Bruce and Kennedy, 1951).

Obesity is not always due to damage to a hypothalamic centre—quite the contrary. It is common experience that people can be divided into two types so far as their weight control is concerned. The first type can apparently commit any dietary indiscretion with impunity and remain like Cassius, lean and hungry looking. No one can dispose of any appreciable quantity of food after it is absorbed without either burning it or storing it as fat. The restless energy of the Cassius type may account for the burning of considerable amounts of food, but his major bouts of overeating must be balanced by periods of reduced intake. I think it is highly

probable that this is brought about, as in the young rat, by the hypothalamus. But the second, less fortunate type of person maintains a steady weight only by conscious attention to his diet, or by early social training which makes such attention a habit. I think this is the type of person who becomes obese. Like the older rat, he has an inefficient hypothalamus, if indeed he has any hypothalamic control at all. Professor McCance and Miss Widdowson (McCance and Widdowson, 1951) have shown that really obese patients are as fat as the fattest rats which can be produced by hypothalamic operation. As such obesity notoriously follows relatively minor causes—emotional upsets and the like—I find it difficult to believe it can be due to paralysis of a major vegetative centre in the hypothalamus. Obesity in such a person has probably a purely cerebral cause and it would be more logical to call it cortical than hypothalamic obesity.

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Captain Albert R. Behnke, M.C., U.S.N.: *Measurement of the Fat and Water Content of the Body in Relation to Obesity.*

The shortening of life expectancy and the many medical ailments that are associated with obesity constitute a long recognized, serious medical problem. The key to an understanding of the problem of obesity would appear to be a quantitative approach centering in the measurement of the fat content of the body. During the past twelve years there have been developed two reliable methods for *in vivo* fat estimation, one based on the determination of the specific gravity of the body as a whole, the other based on the determination of total body water.

The specific gravity of the body as an index of obesity.—Data obtained by naval investigators since 1939 (Behnke, Feen and Welham [1]; Welham and Behnke [2]; Pace and Rathbun [3]) established the close correlation between the specific gravity of the body as a whole and its fat content.

For the determination of specific gravity the essential measurement is that of body volume which, based on Archimedes' principle, can be determined conveniently by the method of hydrostatic weighing, i.e. equivalent volume = weight in air minus weight in water. The weight in water is determined by suspending a subject below the surface of the water on a line leading up to a spring scale graduated in ounces. A weighted lead belt maintains negative buoyancy for all types of persons.

Two weighings in water serve to check the accuracy of the procedure, one at the completion of maximal inspiration and the other at the end of maximal expiration. The difference in weight obtained records hydrostatic displacement which serves as a measure of vital capacity. This determination of vital capacity when corrected for the effect of the mean hydrostatic pressure on thoracic volume gives values comparable to those obtained by the standard method employing spirometry.

The greatest error in the procedure arises from the determination of residual lung volume. If the variation in this measurement is of the order of 200 c.c., values for specific gravity will be subject to an error of $\pm$ 0·003. Repeated determination on the same individual permitting the use of a constant volume for residual air gives values that agree to within 0·003. A second error may arise from the presence of gas in the abdominal viscera. In an attempt to minimize this error, determinations should be made in the morning on the fasting individual.

In the same individual loss or gain of weight in response to a restricted or augmented diet is associated with an increase or decrease in specific gravity of the whole body. The density of the tissue lost or gained can be computed as 0·94, approximately that of fat. From these studies it appeared that there was a simple inverse correlation between the percentage of body fat in relation to total weight and the specific gravity.

The analyses of Rathbun and Pace [4] further established a remarkable quantitative relationship in guinea-pigs between fat content and specific gravity. This relationship, an inverse proportion, is expressed by the correlation coefficient $r = -0{\cdot}97$. These investigators found a range of values for specific gravity similar to those recorded for man, 1·021 to 1·096. The corresponding values for fat content as analysed of the guinea-pigs were 35·8% and 2%.

Uniformity of composition of the lean body mass.—If fat is the chief variable responsible for alterations in specific gravity of the body as a whole, then there must be a remarkable uniformity in the specific gravity of the lean body mass and hence, in the composition of this body mass. Table I indicates the agreement in percentages of water and organic nitrogen in the bodies of various mammalian species.

Measurement of body fat content based on determination of total body water.—If the percentage of water in the lean body mass is constant for healthy adults then it should be possible to estimate the fat content from the determination of total body water. Murray Steele and his co-workers, Messinger, Soberman, *et al.* [5, 6, 7], were able to make satisfactory total body water determinations in man based on the content of injected antipyrine in blood and body fluids. Employing the method of specific gravity as an *independent* estimate of fat content it was found that the percentage of water in the lean body mass was about 72. This is a fundamental value, which if constant for healthy adults, permits an accurate estimate of body fat according to the simple formula,

$$\% \text{ body fat} = \frac{100\,(72 - \% \text{ body water})}{72}$$

TABLE I.—SUMMARY OF MEAN WHOLE BODY WATER AND CHEMICALLY COMBINED NITROGEN CONTENT FOR ADULT MAMMALS

Species	Per cent water	Per cent nitrogen	Per cent fat	Per cent water in lean mass	Per cent nitrogen in lean mass
Rat	65·3	3·54	9·0	71·8	3·89
„	63·6	3·04	14·6	74·4	3·57
„	61·5	3·01	15·3	72·6	3·56
Guinea-pig ..	67·1	3·18	10·0	74·2	3·51
„ ..	63·5	3·08	12·3	72·4	3·52
Rabbit.. ..	69·2	2·91	7·8	73·5	3·09
„	74·3		2·5	76·3	
Cat	66·7	3·22	7·9	72·4	3·50
Dog	59·5		20·01	74·5	
„	59·1		15·4	69·9	
Monkey ..	68·5		6·5	73·3	
Mean				73·2	3·52

Table II gives results obtained for specific gravity and body water on a representative group of 88 adult males.

TABLE II.—RELATIONSHIP IN MAN OF BODY SPECIFIC GRAVITY, BODY FAT AND BODY WATER

Subject	Specific gravity	% Body fat: From spec. gravity	% Body fat: From antipyrine	% Body water: From spec. gravity	% Body water: From antipyrine	% water of lean body mass
1	1·021	39·0	41·5	44·4	43·4	71
2	1·032	33·2	29·0	49·3	51·8	77
3	1·032	27·5	30·4	53·0	50·7	70
4	1·044	27·0	25·2	53·4	53·2	73
5	1·045	26·5	31·0	54·0	50·0	68
6	1·057	20·5	17·2	58·2	60·5	76
7	1·061	18·5	16·3	58·6	58·8	72
8	1·061	18·5	20·4	58·6	58·0	72
9	1·064	17·0	19·9	59·6	58·5	72

Concluding comment.—The concept that the mammalian body consists of a lean body mass of uniform composition is most fundamental and essential in the investigation of many physiological and clinical problems pertaining to metabolism, drug dosage, and muscular function. Since the excess fat content in normal individuals varies from 2 or 3% to 40%, all analytical results relating to body composition and formation must be expressed in terms not of total body weight but of *lean body mass*. Many more analyses are required to determine the percentage of bone and other components and constituents of the lean body mass but it can be inferred from the specific gravity data that not only is the percentage of body water constant, but also cellular water, extracellular water, protein, minerals, essential lipids, blood volume, and the percentage weight of various tissues and organs. Post-mortem analyses of the human body have been too limited as yet to afford reliable data but such analyses are necessary with particular care taken to determine the amount of essential lipid material. The "fat free" body as analysed post mortem by chemical methods is not the same as the lean body mass which is an actual *in vivo* entity which can be quantitated by specific gravity determinations. The procedure of specific gravity is not only applicable *in vivo* and post mortem but it serves to replace and perhaps to measure fat content more accurately than chemical analysis. It is necessary however to utilize both specific gravity and analytical chemical procedures to elucidate further the fundamental concept that healthy mammalian bodies are uniform in composition.

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Dr. E. M. Widdowson and Professor R. A. McCance: *Observations and Estimations of the Total Amount of Fat in the Body.*

A method which has recently been published (McCance and Widdowson, 1951, *Proc. Roy. Soc. B.*, **138**, 115) for determining the total amount of fat in the body was described, and results which have been obtained with it were shown.

Men and women of "normal" weight for height contained about 16–17% of fat. The thinnest healthy man investigated had only 7%. A fat woman weighing 25 st. contained over 60%, i.e. she had 15 st. of fat in her body and the methods used showed that she had no more muscle than the thin man with which to carry this burden about.

When a fat person loses weight, the loss of weight was shown to be due almost entirely to a loss of fat, but when a person of normal weight becomes undernourished there is a loss of muscle as well as fat and at the same time an increase in the proportion of the body occupied by extracellular fluids. This was demonstrated by a study of the rehabilitation of German prisoners of war who had been released from Russian labour camps in 1946–47.

Dr. D. A. W. Edwards: *The Behaviour of Subcutaneous Fat in Lipodystrophy and Lipomatosis.*

Lipodystrophy and diffuse symmetrical lipomatosis are two examples of disorders of subcutaneous fat.

Lipodystrophy is characterized by symmetrical loss of subcutaneous fat from some part of the body, so that in the lipodystrophic areas the subcutaneous tissue layer is so thin that the outlines of the muscles can be clearly seen. The thickness of a fold of skin and subcutaneous tissue is much the same everywhere in these areas, being scarcely greater than that of a fold of the skin alone. This is in contrast to what is found in the normal thin person, where the folds, although thin, vary much more in thickness from place to place. There is clearly a loss of some tissue between the skin and the deep fascia in lipodystrophy. What tissue remains has been examined microscopically by several workers (Christiansen, 1922; Smith, 1921; Weber, 1920; Wells, 1940) who have all found a complete, or almost complete, absence of fat globules. Wells (1940) states that the cells which normally store fat are absent. In contrast to this, in an emaciated person the adipose tissue cells remain and they still contain a small globule of fat although their cytoplasm is reduced in volume. The evidence, therefore, suggests that in lipodystrophy there is a local disappearance of the fat storing cells rather than a local decrease in the amount of fat in each cell.

The opposite condition, diffuse symmetrical lipomatosis, is characterized by a symmetrical abnormal increase in the amount of subcutaneous fat in some part of the body. Microscopically the excess tissue is similar to normal fat without any obvious increase in the non-fatty constituents. Moreover, its response to changes in the total storage fat of the body is the same as normal fat. This can be shown quite simply in the following way. If an obese woman is put on a reducing diet, and, as she loses weight, the thickness of the fat is measured by the fold method, it is found that the thickness decreases at the same rate over the whole body. In other words, if the thickness of the fat at one place is halved, it is halved everywhere. The same thing happens in lipomatosis, so that when the thickness of the normal tissue is halved, the thickness of the area of lipomatosis is halved at the same time (Edwards, 1951*a*). Although normal parts of the body may in this way become quite slim or even very thin, the areas of lipomatosis remain abnormal in shape and plump in proportion to the rest of the body, because the pattern of distribution of the fat remains the same, however much total fat there is. When the normal parts of the body carry an average amount of fat a lipomatotic leg may not attract much attention or at least the disorder may not be diagnosed.

There are two interesting points about this excessive fat. Firstly, the thickness is nearly equal all the way down the limb as far as the wrist or ankle. This is in contrast to the normal pattern, in which the fat is much thicker at the proximal end of the limb than at the distal end. Secondly, this new pattern of distribution of the fat along the limb is very similar from one patient to another, so that the increase in thickness does not seem to be a random process, but occurs according to a fixed pattern, which is quite different from the normal distribution pattern (Edwards, 1951*a*).

Now this increase in fat might occur in either of two ways. There might be more fat in each cell, without any change in the number of cells. On the other hand, there might be more cells, each containing a normal amount of fat. The answer to this problem was obtained in the following way.

It has been found that subcutaneous fat cells from different places on the same person appear to contain about the same amount of fat, judging by the average size of the cavities in the cells seen in paraffin sections. Similarly, it has been found that if the average size of the cavities in fat cells from different people, but from the same place on the body, are compared, then the fatter the person is the more fat there is in each cell, and there is a simple proportional relationship between the thickness of the layer of subcutaneous fat at a given place, and the amount of fat in the cells (Edwards, 1951*b*).

Samples of abnormal tissue were obtained from the legs of two patients with lipomatosis, but unfortunately samples of normal tissue were not taken from them at the same time. The observations on normal tissue were therefore used to get a rough idea of what the cells of the patient's normal tissue would look like. This was done by measuring the thickness of fat in the normal areas of the patients, then finding cadavers with similar measurements.

When the cells of the abnormal tissue are compared with cells from normal tissue of the same or another region of a cadaver, of the same general build as the patient, the average size of the cavities in the various tissues appears to be very much the same, so that, because the thickness of the abnormal tissue is much greater than that of the normal, the difference in thickness must be due to a difference in the number of cells, since the amount of fat in the cells is the same.

Here, then, are two disorders of fat-storing tissue. In lipodystrophy there is apparently a local disappearance of the fat-storing cells, and in lipomatosis an increase in their number. In lipomatosis, once the new cells have been developed, they behave normally to changes in the amount of body fat and seem to contain the same amount of fat as the other subcutaneous tissue fat cells of the body. The two conditions seem to be disorders of numbers of fat cells rather than functions of fat cells.

But perhaps the most surprising observation of all is that both these disorders commonly occur together in the same patient.

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